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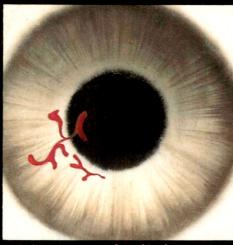


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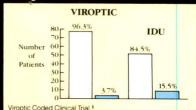
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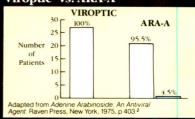


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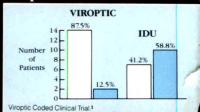
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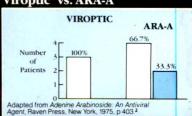
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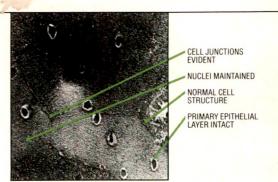
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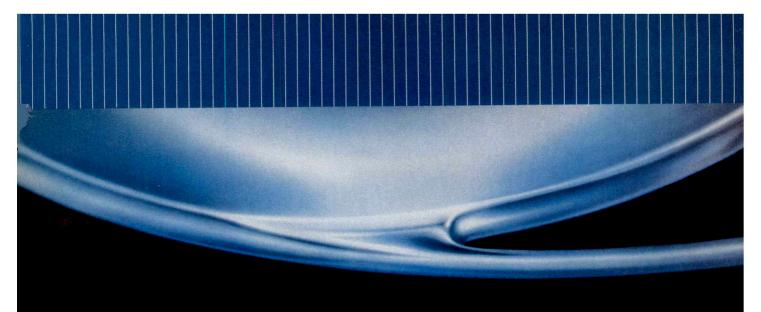
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Ocular Syphilis in Patients With Human Immunodeficiency Virus Infection

Michael S. Passo, M.D., and James T. Rosenbaum, M.D.

We diagnosed ocular syphilis in three homosexual men infected with human immunodeficiency virus (HIV). Ocular inflammation included uveitis, optic neuritis, and retinitis. Dermatologic and central nervous system manifestations of secondary syphilis were also present. The history of homosexuality was difficult to obtain. Concomitant infection with HIV may alter the course of syphilis, obscure the diagnosis, and impair the response to therapy.

PATIENTS AT RISK for sexually transmitted human immunodeficiency virus (HIV) infection are also at risk for other sexually transmitted diseases, such as syphilis. However, in seven separate reviews of the ocular manifestations of the acquired immunodeficiency syndrome (AIDS), syphilis was not noted among the 235 patients described. Several individual case reports have noted the coexistence of ocular syphilis and AIDS. 143

Recent reports of syphilis in HIV-infected individuals indicate a severe, accelerated course of syphilis that frequently involves the central nervous system and often does not

respond to standard therapy for primary and secondary syphilis. ¹³⁻¹⁵ Infections with *Trepone-ma pallidum* may easily be confused with other manifestations of HIV infection. Since syphilis is a treatable infection, its recognition has obvious therapeutic implications.

We describe three HIV-infected patients with ocular syphilis.

Case Reports

Case 1

A 42-year-old man was referred for ophthalmologic evaluation of retrobulbar pain and epiphora in the left eye on May 23, 1985. Five months earlier he had developed malaise, fatigue, lymphadenopathy, and a pruritic macular skin rash on his forearms and trunk. A biopsy of an inguinal lymph node showed reactive hyperplasia. Visual acuity was 20/20 in both eyes, with chemosis, epiphora, and optic nerve edema of the left eye. One week later his ocular symptoms had almost completely resolved. Examination disclosed a 0.6-log unit afferent pupillary defect in his left eye associated with an enlarged blind spot and mild depression of central visual function (Fig. 1), as well as edema of the peripapillary nerve fiber layer with venous engorgement.

Four weeks later pain and blurred vision recurred in his left eye. Visual acuity had decreased to 20/70 in the left eye, with 4+ cell and flare in the anterior chamber, and many precipitates and posterior synechiae. The left disk remained swollen. In the right eye, the fundus was normal. A rare cell was present in the anterior chamber. A regimen of topical corticosteroids and cycloplegics was initiated.

Results of a biopsy of adenoidal tissue dem-

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From the Department of Ophthalmology, Veteran's Administration Hospital (Dr. Passo) and the Departments of Internal Medicine, Ophthalmology, and Cell Biology (Dr. Rosenbaum), Oregon Health Sciences University, Portland, Oregon. This study was supported in part by Research to Prevent Blindness, Inc., and National Institutes of Health grant EY06484. This research was performed while Dr. Rosenbaum was a Dolly Green Scholar sponsored by Research to Prevent Blindness, Inc.

Reprint requests to Michael S. Passo, M.D., Department of Ophthalmology, L467, Oregon Health Sciences University, 3181 S.W. Sam Jackson Park Rd., Portland, OR 97201.

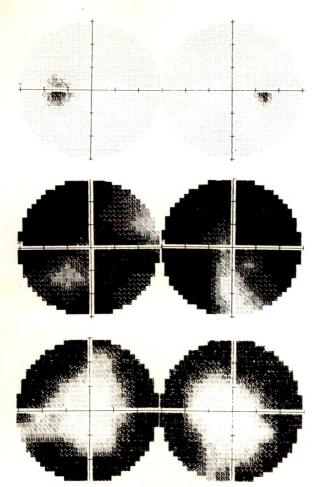


Fig. 1 (Passo and Rosenbaum). Case 1. Top, Visual field from May 29, 1985, showing an enlarged blind spot in the left eye and slightly reduced visual function when compared to the normal right eye. Middle, Repeat visual fields from Sept. 19, 1985, showing near total depression of the central 30 degrees bilaterally. Bottom, One year after the initial visual field, both fields are still remarkably constricted to within the central 20 degrees.

onstrated granulomatous inflammation, possibly involving a blood vessel. A tentative diagnosis of Wegener's granulomatosis was made, and a treatment regimen of 60 mg of oral prednisone per day was started. Some improvement was seen in the uveitis, with visual acuity stabilizing at R.E.: 20/20 and L.E.: 20/40 one week later.

Three weeks after oral prednisone was started, the uveitis worsened and areas of retinal necrosis were noted. Visual acuity had deteriorated to R.E.: 20/200 and L.E.: counting fingers at 2 feet. A bilateral panuveitis was manifested

by anterior chamber cell and flare; edematous and pale disks, with peripapillary sheathing of retinal vessels; and many small, white subretinal deposits scattered throughout the equator in both eyes (Fig. 2, left). Visual field examination demonstrated severe constriction to within 20 degrees centrally in each eye (Fig. 1). Fluorescein angiography disclosed mild bilateral disk edema and striking diffuse, well-circumscribed hyperfluorescence extending along the superior and inferior vascular arcades into the fovea bilaterally (Fig. 3). Small punctate pigment epithelial defects were present peripherally, which corresponded to the white subretinal defects seen clinically.

An infectious disease consultant obtained a history of contact with male prostitutes. The patient denied intravenous drug use and had never received a transfusion of blood products. He was allergic to penicillin. On physical examination a macular/papular, blotchy, erythematous rash was noted on his chest, abdomen, forearms, palms, and soles (Fig. 4).

Laboratory examination disclosed a positive rapid plasma reagin titer of 1:128 and reactive FTA-ABS test. Cerebrospinal fluid examination showed a reactive FTA-ABS at a dilution of 1:2, a total protein level of 66 mg/100 ml, a glucose level of 47 mg/100 ml, and a blood cell count of 250 red blood cells and 13 white blood cells/mm³ (11 lymphocytes, one polymorphonuclear, and one monocyte). He had a strongly positive HIV antibody titer (enzyme-linked immunosorbent assay) with a P-32 band by Western blot analysis.

A diagnosis of secondary syphilis was made. Because of the patient's allergy to penicillin and central nervous system involvement, he was given 2 g of chloramphenicol per day for 14 days. His rash worsened over the next two days despite 80 mg of oral prednisone daily. By day 5, the rash had faded and the retinal lesions began to disappear. Over the next four weeks, the uveitis resolved and visual acuity improved to R.E.: 20/50 and L.E.: 20/100. Diffuse pigment epithelial mottling was present bilaterally, with a salt-and-pepper fundus appearance.

On Nov. 14, 1985, a rhegmatogenous retinal detachment caused an acute loss of vision in his left eye. After a scleral buckling procedure, the retina remained attached. When last seen on Dec. 17, 1987, visual acuity was R.E.: 20/20 and L.E.: 20/60. Both anterior chambers were quiet, with a posterior subcapsular cataract on the left. Occasional cells persisted in the vitreous bilaterally, and marked generalized depigmen-

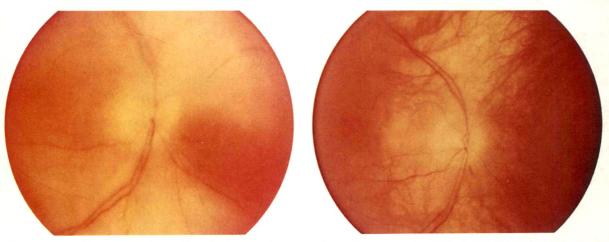


Fig. 2 (Passo and Rosenbaum). Case 1, fundus photographs of the left eye. Left, Sept. 19, 1985, the disk is pale and edematous. White areas of retinitis are evident. The view of the fundus is generally hazy. Right, May 21, 1986, the optic disk is pale. Vessels are attenuated. Atrophy of the pigment epithelial layer has occurred with prominence of the choroidal circulation.

tation was present throughout the fundus. Both disks were pale (Fig. 2, right). Visual fields remained constricted to the central 20 degrees (Fig. 1).

Case 2

A 38-year-old homosexual man developed malaise and lymphadenopathy in June 1985. Four months later, after development of a rash

Fig. 3 (Passo and Rosenbaum). Case 1, left eye. Late phase fluorescein angiogram demonstrates disk edema and diffuse, well-circumscribed hyperfluorescence extending along the vascular arcades into the fovea.

on his elbow, results of a VDRL and HIV antibody titer were negative. T cell subsets were normal. The rash waxed and waned for the next nine months and at times involved his palms and soles. After dermatologic consultation, a working diagnosis of psoriasis was made. A regimen of topical corticosteroids was instituted with minor success. He returned to his internist in October 1986 with headaches, weight loss, blurry vision, and complaints of floaters. At this time his HIV antibody titer was positive and a diagnosis of AIDS-related complex was made.

On initial ophthalmologic examination on Dec. 19, 1986, visual acuity was R.E.: 20/50 and L.E.: hand motions. Bilateral fine keratic precipitates with endothelial edema were present.

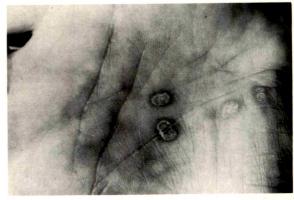


Fig. 4 (Passo and Rosenbaum). Case 1. Palmar rash typical of late secondary syphilis.

Both eyes had cells in the aqueous and vitreous humor. Macular edema was present bilaterally. After a three-month regimen of topical and subconjunctival corticosteroids visual acuity improved to 20/60 in both eyes.

In April 1987, an evaluation for possible systemic causes of the uveitis was begun. Results of laboratory studies included a positive VDRL with a 1:256 titer and a 3+ FTA-ABS. Examination of cerebrospinal fluid showed hazy fluid with a 1:16 VDRL and a total protein level of 153 mg/100 ml, a glucose level of 49 mg/100 ml, and 410 white blood cells/mm³ with 93% lymphocytes. Both HIV antibody titer and Western blot analysis were positive. He was treated with 2.4 million units of intravenous penicillin G every four hours for the next ten days, and then 2.4 million units of penicillin G benzathine intramuscularly every week for three weeks.

Almost immediately his rash and uveitis improved. By July 22, 1987, all medications had been discontinued. He gained 20 pounds and visual acuity improved to 20/20 in both eyes, with quiet anterior chambers and vitreous. His pupils remained dilated and nonreactive (R.E.: 8 mm and L.E.: 7 mm in diameter). Repeat serologic studies showed the VDRL had decreased to 1:64, with the FTA-ABS still strongly positive at 4+. T cell helper:suppressor ratio in the peripheral blood was 0.42.

Six weeks later, vision in his left eye was blurry, with an associated dull ache. Examination showed a moderate amount of inflammation in the anterior chamber. A repeat serum VDRL was 1:64. The cerebrospinal fluid VDRL had declined to 1:2, with a total protein level of 36 mg/100 ml, a glucose level of 49 mg/100 ml, and 5 white blood cells/mm³ (all lymphocytes). The uveitis responded to topical prednisolone acetate 1% four times a day. When last seen on Dec. 12, 1987, visual acuity was 20/20 in both eyes, with 6-mm reactive pupils (light and accommodation) and no evidence of active uveitis.

Case 3

A 27-year-old bisexual man with a history of intravenous drug use was referred for evaluation of uveitis by his local ophthalmologist on Dec. 22, 1986. Approximately two weeks previously, the patient noted periorbital pain, eye redness, and many large floaters affecting the left more than the right eye. These symptoms waxed and waned. The patient reported an episode of sterile meningitis one year previous-

ly and a negative HIV test in July 1986. Several months before initial examination, the patient received a course of amoxicillin for presumed athlete's foot. The patient denied any sexual experiences for the past year and claimed to have used intravenous drugs only once in the past six months.

The general physical examination showed diffuse lymphadenopathy. The skin showed an erythematous, hyperkeratotic rash over his palms and soles. These skin changes had been present for some time and were previously ascribed to a local fungal infection.

On ophthalmic examination, visual acuity was R.E.: 20/15 and L.E.: 20/40 with pinhole improvement to 20/30. Abnormal findings included a few small keratic precipitates distributed inferiorly in the left eye. The left anterior chamber had 1+ cell and flare, with pigment dusting of the anterior lens capsule. Cells were present in the vitreous bilaterally, with large vitreous opacities seen only on the left. The disk margins were blurred. No retinal or pars plana exudates were present. Treatment was initiated with topical corticosteroids and cycloplegics. Serologic tests for syphilis showed a serum VDRL titer of 1:64 and a 4+ reactive serum FTA-ABS. Cerebrospinal fluid examination demonstrated a VDRL titer of 1:2, total protein level of 44 mg/100 ml, a glucose level of 49 mg/100 ml, and there were 22 lymphocytes, five mononuclears, three polymorphonuclears, and no red blood cells/mm3. Serum HIV antibody titer was positive by both enzyme-linked immunosorbent assay and Western blot analysis (band in P-24 and P-41 regions).

The patient was hospitalized and treated with 2.4 million units of intravenous penicillin G, every four hours for ten days. After discharge, he received 2.4 million units of intramuscular penicillin G benzathine weekly for three weeks.

Approximately one year after treatment, the patient was examined in an emergency room because of bilateral floaters. Visual acuity was 20/20 in both eyes, the pupils were normal, and the anterior chambers were quiet. Vitreous opacities were present bilaterally, but they were not believed to represent active inflammation. No retinal or pars plana exudates were seen. On cerebrospinal fluid examination, the VDRL was negative, the total protein level was 36 mg/100 ml, the glucose level was 48 mg/100 ml, and there were three cells/mm³ (all lymphocytes). The patient was lost to follow-up.

Discussion

In each of these three HIV-infected patients with ocular syphilis, the ocular disease was associated with cutaneous manifestations and markedly abnormal cerebrospinal fluid; the diagnosis of syphilis was not initially suspected, and one patient (Case 1) consulted ten physicians, including seven specialists, before the diagnosis was established; and there was no history of opportunistic infection in association with the HIV infection. Therefore, these three patients did not have AIDS, although the manifestations of syphilis were sometimes mistaken for AIDS.

The following factors may have contributed to the failure to make the correct diagnosis: (1) since syphilis is a rare cause of uveitis, ophthalmologists frequently overlook it16; (2) HIV infection may alter the serologic response to syphilis14 (Patient 2 had a negative VDRL despite his active rash); (3) results of biopsy of affected skin or lymphatic tissue may lead to a mistaken diagnosis, as in Case 1; (4) patients frequently deny a history of homosexuality or drug use; (5) a diagnosis of HIV infection may have dissuaded physicians from looking for a treatable cause of uveitis, as in Case 2; (6) a history of chancre or primary infection may be absent, as in all three of these patients; and (7) spontaneous improvement or response to corticosteroids may suggest that the ocular disease is noninfectious, as in Cases 1 and 2.

All patients were treated successfully with antitreponemal therapy for ten days, as is suggested for neurosyphilis. 17 Reports of failures with standard treatment of secondary syphilis13,14 and the unresolved issue of how the coexistence of syphilis and HIV infection affects the other's natural course^{13,14} were considerations for the choice of therapy and adequacy of follow-up. The potential for immunosuppression in both syphilis 18 and HIV infections 19 makes incomplete eradication potentially more likely. In two of the cases presented here, ocular symptoms recurred after treatment for syphilis. In Patient 2, a recrudescence of anterior uveitis was associated with a fourfold decrease in cerebrospinal VDRL and was easily treated with topical ocular corticosteroids. Patient 3 developed vitreous floaters one year after treatment for syphilis in association with a negative cerebrospinal fluid VDRL. While the uveitis in Patient 2 was probably an immunerelated recurrence, close follow-up will be necessary to rule out recurrent syphilis or other HIV-related manifestations.

The combination of syphilis and HIV infection can alter the diagnosis and treatment of each of these conditions. ¹²⁻¹⁴ Patients with rapid plasma reagin positivity may show false positivity on enzyme-linked immunosorbent HIV testing. ²⁰ This false positivity is usually low titer and associated with a negative Western blot analysis. Seronegative secondary syphilis has also recently been reported in a patient with Kaposi sarcoma and HIV infection. ¹⁴ Diagnosis in this patient required direct testing for spirochetes from skin biopsy material.

The incidence of ocular complications and neurosyphilis may be increased with HIV infection. All patients with syphilis should be tested for HIV antibodies and vice versa.21 If the patient is positive for HIV antibody (by enzymelinked immunosorbent assay and Western blot analysis) or if the patient has secondary syphilis, we recommend examination of the cerebrospinal fluid to rule out neurosyphilis. If there is evidence for neurosyphilis, monthly clinical examination and serologic testing should be done for one year. Cerebrospinal fluid should be examined every six months for three years.²² Retreatment is recommended in initial primary and secondary syphilis when there is less than a fourfold decrease in the VDRL titer by three months, or a sixfold decrease at six months. 23 In neurosyphilis, retreatment is indicated if there is an increase in the cerebrospinal fluid blood cell count.24

Further studies may show that chronic therapy is indicated in some HIV-infected patients. ¹³ Careful follow-up by public health officials should also include investigation of sexual contacts with treatment based appropriately.

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OPHTHALMIC MINIATURE

In the other direction . . . was Watkin, the Classics Professor, a man of terrifying dryness and oddity. His heavy rimless glasses were almost solid cubes of glass within which his eyes appeared to lead independent existences like goldfish.

Douglas Adams, Dirk Gently's Holistic Detective Agency New York, Pocket Books (A Division of Simon and Schuster), 1987, p. 22

Response of Human Immunodeficiency Virus-Associated Uveitis to Zidovudine

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A patient with human immunodeficiency virus (HIV) type 1 infection developed chronic iridocyclitis and anterior vitritis that were poorly responsive to topical and systemic corticosteroid therapy. Anterior chamber paracentesis was performed and HIV was isolated from culture of aqueous humor. Subsequent treatment with oral zidovudine resulted in resolution of the iridocyclitis and vitritis and full functional recovery of the eye. This case suggests that HIV may be a cause of uveitis responsive to systemic zidovudine therapy.

COMMON OCULAR manifestations of the acquired immunodeficiency syndrome (AIDS) include retinal microangiopathy, opportunistic retinal necrosis (most commonly caused by cytomegalovirus), Kaposi's sarcoma of the conjunctivae and eyelids, and herpes zoster ophthalmicus.1-4 More rarely, opportunistic intraocular infections caused by mycobacteria, Toxoplasma gondii, other herpes viruses such as herpes simplex, and fungal species such as Cryptococcus neoformans and Candida albicans have been reported. 5-7 HIV has been isolated from tears,8 conjunctival epithelium,9 cornea,10 iris, retina, and vitreous, 11 as well as from brain and cerebrospinal fluid. 12

Zidovudine is a nucleoside analogue that appears to prolong survival in a subset of patients with AIDS and has been shown to inhibit the infectivity of HIV in vitro. 13 Little is known about the ocular pharmacodynamics of zidovudine, but the drug is known to cross the blood-brain barrier and positive effects have been claimed in some patients with HIVassociated neurologic disease.14 We studied a case of HIV-associated uveitis that responded to oral zidovudine therapy.

Case Report

A 36-year-old man, who was a former intravenous drug abuser, had a two-week history of irritation of the left eye. During a routine medical examination two months earlier, he was found to be HIV-positive. Examination of the left eye demonstrated a visual acuity of 20/50, moderate epibulbar injection, an irregular but reactive pupil, mutton-fat keratic precipitates, a brisk cell and flare reaction in the anterior chamber, and evidence of posterior synechiae between the iris and lens. Results of ophthalmoscopy were normal. No abnormalities were found in the right eye. Initial laboratory evaluation included complete blood cell count with differential, erythrocyte sedimentation rate, VDRL, fluorescent treponemal antibody absorption test for syphilis, Sabin Feldman dye test, serum antibody titers to cytomegalovirus and herpes simplex virus, blood and urine cultures for cytomegalovirus, and a chest roentgenogram. Results of all studies were normal or noncontributory. Purified protein derivative was nonreactive with positive controls. Initial ocular treatment included topical prednisolone acetate 1% applied every two hours and topical cycloplegia.

One week later visual acuity had decreased to 20/200. Increased cell and flare reaction was noted in the anterior chamber and there were signs of vitreal inflammation. Oral prednisone, 40 mg daily, was added to the treatment regi-

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men. After one week of combined oral and topical corticosteroid therapy, visual acuity returned to 20/50 but the anterior chamber and vitreous inflammation persisted. Over the ensuing weeks, several unsuccessful attempts were made to taper the systemic corticosteroid therapy. T-lymphocyte studies were performed at this time (Table).

Eleven weeks after the initial examination, the patient underwent anterior chamber paracentesis and the aqueous fluid was sent for HIV culture. At this time 100 mg of oral zidovudine four times daily was started and the topical prednisolone was tapered. Specular microscopy demonstrated many white blood cells adherent to the posterior surface of the corneal endothelium. After a ten-day regimen of oral zidovudine, the intraocular inflammation had decreased markedly. Because results of blood cell counts were normal, the zidovudine was increased to 200 mg every four hours. After two weeks of higher-dose zidovudine treatment, visual acuity was 20/20 and only trace cells were visible in the anterior chamber by slit lamp biomicroscopy. Specular microscopy showed complete disappearance of white blood cells on the corneal epithelium.

Blood cell counts and T-lymphocyte studies were closely monitored after the initiation of zidovudine treatment in order to assess both the extent of any drug-induced toxicity and the beneficial effect on T-cell populations. The patient's blood cell counts remained normal while the number of T-helper cells remained depressed (Table).

TABLE T CELL PROFILE

_	2 MOS BEFORE ZIDOVUDINE	ZIDOVUDINE BEGUN	3 WKS AFTER ZIDOVUDINE	
White blood cell				
count/mm ³	5,300	4,400	4,000	
Lymphocyte				
count/mm ³	1,900	2,100	2,100	
Total T cells/mm ³	1,571	1,763	1,766	
Total helper				
T cells/mm ³	366	375	459	
Total suppressor				
T cells/mm ³	980	1,190	1,264	
Helper/				
suppressor ratio	0.37	0.31	0.36	

Material and Methods

Paracentesis of the anterior chamber at the corneoscleral limbus was performed under a microscope using a 27-gauge needle and yielded approximately 0.2 ml of aqueous humor. The aqueous was inoculated directly onto phytohemagglutinin-stimulated peripheral blood mononuclear cells (1 \times 10 6 /ml) from an HIV-negative donor. The cultures were carried in 25-cm² tissue culture flasks in 10 ml of RPMI 1640 medium supplemented with 20% fetal calf serum, 2 μg/ml polybene, 10% interleukin-2, 5 to 10 neutralizing units of anti-alpha interferon, 100 μl/ml of penicillin G, and 100 μg/ml of streptomycin. Cultures were observed for signs of syncytium formation, refed with cells, and the medium was changed weekly. Culture supernatants were assayed for HIV p24 core antigen by an enzyme-linked immunosorbent assay capture method.

Ophthalmologic procedures included measurement of visual acuity, slit-lamp biomicroscopy, and indirect ophthalmoscopy. Specular microscopy of the corneal endothelium was performed with a wide-field specular microscope. ¹⁵

Results

This HIV-infected former intravenous drug abuser developed a chronic iridocyclitis and vitritis. Aqueous humor culture supernatants contained 220 pg of HIV p24 antigen/ml after 13 days' incubation. Ocular inflammation resolved and visual acuity improved markedly after a course of oral zidovudine was initiated.

Discussion

The high incidence in AIDS of retinal microangiopathy, characterized by cotton-wool spots and hemorrhage, Kaposi's sarcoma of the conjunctiva and ocular adnexa, and cytomegalovirus retinitis has been reported by many investigators. ¹⁻⁷ Iridocylitis and vitritis are seen in patients with AIDS but usually in association with opportunistic intraocular infection or herpes zoster ophthalmicus. In addition to cytomegalovirus retinitis, other ocular infections known to complicate AIDS and cause iridocycli-

tis and vitritis are recrudescent toxoplasmosis, mycobacterial choroiditis, fungal choroiditis (*Cryptococcus* or *Candida*), and herpes simplex retinitis.⁵ In our patient, no evidence of concomitant opportunistic intraocular infection, either on a serologic or physical basis, could be found.

HIV is neurotropic and has been implicated as a causative factor in AIDS-related neurologic disease. 16-18 It has been isolated from brain tissue and cerebrospinal fluid, and in a recent report, three of four patients with AIDS-related neurologic disease improved with oral zidovudine therapy. 14 It is well known that HIV can be isolated from the external eye (tears, cornea, and conjunctival epithelium), 8-10 but only recently has the virus been isolated from intraocular structures including iris, retina, and vitreous. 11 HIV has not, however, been demonstrated to cause ophthalmologic disease directly, although Pomerantz and coworkers19 have implicated HIV infection of the retina as an etiologic factor in AIDS-associated retinal microangiopathy. We believe that the isolation of HIV from the aqueous humor of our AIDS patient with iridocyclitis and vitritis, but without evidence of opportunistic intraocular infection, and the rapid response to oral zidovudine suggests that HIV may directly cause intraocular inflammation and dysfunction.

It is possible, however, that the iridocyclitis and vitritis in this patient were caused by an unidentified opportunistic pathogen. Furthermore, the presence of HIV in the aqueous humor may be coincidental to the uveitis. Colonization of the aqueous humor may also be the result of the inflammation, which can cause a breakdown in the blood-ocular barrier and allow an influx of HIV-infected lymphocytes. A particular subset of AIDS patients and those with AIDS-related complex who are treated with zidovudine develop significantly fewer opportunistic infections and have a four- to sixfold decreased death rate at nine months of therapy.13 That this patient's ocular status improved while receiving zidovudine therapy could be ascribed to an overall improvement in immune competence, but it was more likely the result of an antiviral effect of the drug since neither absolute T cell counts nor helper/ suppressor ratios changed significantly during the interval when the uveitis cleared.

Since HIV is known to be neurotropic within the central nervous system, it is highly likely that intraocular structures, especially the retina and optic nerve, may be damaged by the virus. HIV may be an etiologic factor in AIDS-associated uveitis of unknown origin and such inflammations may respond to oral zidovudine therapy.

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OPHTHALMIC MINIATURE

"So, young MacDuff," said the Professor once he was seated and flapping his napkin open, "pleasure to see you again, my dear fellow. Glad you could come. No idea what all this is about," he added, peering around the hall in consternation. "All the candles and silver and business. Generally means a special dinner in honor of someone or something no one can remember anything about except that it means better food for a night."

He paused and thought for a moment, and then said, "It seems odd, don't you think, that the quality of the food should vary inversely with the brightness of the lighting. Makes you wonder what culinary heights the kitchen staff could rise to if you confined them to perpetual darkness. Could be worth a try, I think."

Douglas Adams, Dirk Gently's Holistic Detective Agency New York, Pocket Books (A Division of Simon and Schuster), 1987, p. 14

Normal α-L-Fucosidase and Other Lysosomal Enzyme Activities in Progressive Cone Dystrophy

Vasiliki D. Stoumbos, M.D., Richard G. Weleber, M.D., and Nancy G. Kennaway, D. Phil.

We conducted a cross-sectional study of 24 patients with cone dystrophy to investigate a possible link between this disease and deficient activity of α-L-fucosidase. We studied patients with several forms of cone dystrophy, including six with similar clinical characteristics to two patients previously reported to be α-L-fucosidase deficient. Activities for α-L-fucosidase and several other lysosomal enzymes (β-D-glucuronidase, β-D-hexosaminidase (A + B), and α-D-mannosidase) were determined in serum and leukocytes. None of our patients with cone dystrophy were deficient in α-L-fucosidase or any other lysosomal enzyme investigated. No relationship was found between α-L-fucosidase deficiency and any type of cone dystrophy studied.

THE CONE DYSTROPHIES are a heterogeneous group of retinal degenerative diseases that have been defined by several shared clinical characteristics. Patients show progressive deterioration of central visual acuity, photophobia, impaired color discrimination, and abnormalities of cone-mediated responses of the electroretinogram. 1-3 Krill1 described three clinical patterns in the fundus: the most common type is a bull's-eye pattern of pigment epithelial atrophy, and the less common variants are diffuse pigment clumping and choroidal vascular atrophy. Normal fundi can also be seen early in the course of the disease or in variant forms of cone dystrophy.2-4

Although clinical characteristics of cone dystrophy have been well described, little is known about the underlying pathophysiologic defects. Subclassification has therefore been based on patterns of retinal elements involved or on inheritance patterns. Some patients show abnormalities of cone function only, while others show involvement of both rods and cones. Defects may be diffuse or localized to the central or peripheral retina. Inheritance patterns include autosomal dominant, autosomal recessive, X-linked recessive, and sporadic, with clinical and functional manifestations tending to be similar within any given family. The various patterns of inheritance and photoreceptor involvement indicate heterogeneity within the group of cone dystrophies. Since there have been few investigations involving patients with cone dystrophy, little is known about the metabolic or pathophysiologic differences between these groups. Hayasaka and associates5 recently studied 44 patients with cone dystrophy, including two with autosomal dominant inheritance and two sporadic cases. They reported levels of α-L-fucosidase activity in leukocytes that were half those of normal in the two sporadic cases. To investigate this finding, we conducted a similar study involving 24 patients with various forms of cone dystrophy and ten normal control subjects. We measured α-L-fucosidase, activities of glucuronidase, β-D-hexosaminidase (A + B), and α -D-mannosidase in serum and leukocytes.

Subjects and Methods

Records of patients with cone disorders were selected from the patient registry of the Oregon Retinitis Pigmentosa Center at our institution. Seventy-nine patients were examined between January 1977 and September 1986 in whom a final diagnosis of cone degeneration, cone dystrophy, or cone-rod dystrophy had been made and who had ganzfeld electroretinograms3,6 to

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From the Departments of Ophthalmology (Drs. Stoumbos and Weleber) and Medical Genetics (Drs. Weleber and Kennaway), Oregon Health Sciences University, Portland, Oregon. This study was supported in part by the National Retinitis Pigmentosa Foundation Fighting Blindness, Baltimore, Maryland.

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support the diagnosis. Charts of all 79 patients were reviewed, and 34 were found with strong clinical evidence to support the diagnosis of progressive cone or cone-rod dystrophy. All 34 had cone dysfunction evident by both electroretinogram and other means of testing cone function, including performance on AO H-R-R color plates, Nagel anomaloscope testing, Farnsworth Panel D-15, or Farnsworth-Munsell 100-Hue tests. Electroretinograms showed abnormalities of cone-mediated responses, with rod-mediated responses being normal or mildly subnormal. Patients with stable disease, disease thought to be present since birth, or a history of exposure to drugs known to cause cone dysfunction, were excluded. The 34 patients included three sibling pairs, and only one sibling from each pair was selected for recruitment into the study. An additional seven patients could not be contacted, declined to participate, or had died, leaving 24 patients who signed informed consent and participated in the study. Ten normal volunteers were also recruited as controls. The protocol was approved by our institutional Human Studies Ethics Committee.

Of the 24 patients with cone dystrophy, there were 14 males (aged 8 to 64 years; average, 31.0 years) and ten females (aged 7 to 49 years; average, 32.2 years). Twenty patients had generalized cone dystrophy and four had localized macular cone dystrophy similar to the entity described by Deutman⁷ as benign concentric annular macular dystrophy. By inheritance pattern, five patients had autosomal dominant cone dystrophy, three had X-linked recessive cone dystrophy, four had autosomal recessive cone dystrophy (known affected siblings or parental consanguinity), and 13 cases were sporadic (no known affected family members, but possibly representing autosomal recessive inheritance or new mutations). Six patients had normal-appearing fundi, electroretinogram abnormalities involving only cone-mediated responses (with normal rod-mediated responses), and other clinical characteristics similar to those described by Ohba4 and Hayasaka and associates in patients with an unusual form of progressive cone dystrophy and low α-Lfucosidase activity. Three of our patients had a clear autosomal recessive inheritance pattern and three were sporadic, whereas the previously described patients were all sporadic.

Four men and six women served as controls for the lysosomal enzyme assays (aged 30 to 62

years; average, 38.9 years). None had symptoms of retinal dystrophy or any family members known to be affected with retinal dystrophy or lysosomal storage diseases.

Heparinized and nonheparinized samples of fasting venous blood were collected from each patient and control. Serum was separated from nonheparinized blood by centrifugation. Leukocytes were isolated from heparinized blood by sedimentation in 3% dextran and lysis of erythrocytes with distilled water.8 After separation into components, all samples were stored at -20 C until enzymatic assays were run. Leukocyte pellets were suspended in distilled water and sonicated for 50 seconds before assay. Serum and leukocyte preparations from all patients and nine of ten controls were randomized before assay. Replicate samples from the one unrandomized control were tested each time the enzyme assays were run to check for day-to-day variations in test results. The average percent deviation from the mean was 7.1% for the α -L-fucosidase assay in all patients and controls. Similar day-to-day variations were seen for the other enzymatic assays (6.8%, 7.0%, and 6.6% for β-D-glucuronidase, β-Dhexosaminidase (A + B), and α -D-mannosidase assays, respectively).

activities of α -L-fucosidase, glucuronidase, β -D-hexosaminidase (A + B), and α-D-mannosidase were determined in serum and sonicated leukocyte suspensions. Samples were incubated with methylumbelliferone conjugated substrates, and the amount of 4-methylumbelliferone released was determined fluorimetrically.8,9 All assays were run concurrently with blanks consisting of enzyme sample incubated separately from substrate to correct for autofluorescence of serum or leukocyte preparations. Enzyme activity was expressed as nanomoles of 4methylumbelliferone released per hour per milliliter of serum or per milligram of leukocyte protein. Protein measurements were made by using the method of Lowry and associates10 on sonicated leukocyte preparations.

Results

The activity of α -L-fucosidase was 65.6 \pm 21.5 nmol/hour/mg protein (mean \pm 2 S.D.) in normal volunteers and 71.9 \pm 16.8 nmol/hour/mg protein in adult patients (P > .05 by two-tailed

Student's t-test). No patient showed activity significantly below the normal range. Similarly, there were no statistically significant differences between control and patient values for β-Dglucuronidase (controls, 338 ± 51 and adult patients, 368 ± 84 nmol/hour/mg protein; P > .05), β-D-hexosaminidase (A + B) (controls, $1,666 \pm 731$ and adult patients, $1,716 \pm 594$ nmol/hour/mg protein; P > .05) or α -D-mannosidase (controls, 119 \pm 62 and adult patients, 123 ± 74 nmol/hour/mg protein; P > .05) (Figure). Neither the patient group as a whole nor any individual patient fell significantly below the control group's range for any enzyme activity tested. Comparable results were obtained for serum enzyme activity levels (data not shown). All four patients under age 15 years tended to show increased activities of all enzymes tested. This may be typical for their

age group.

Enzyme activities from our normal group were compared with values from Group 1 (mild myopia) in the study done by Hayasaka and associates after conversion of their units (µg p-nitrophenol released/hour/mg protein) to nmol p-nitrophenol released/hour/mg protein. For α-L-fucosidase in leukocytes, our range was 47 to 82 nmol 4-methylumbelliferone released/ hour/mg protein, whereas the previous study found a range of approximately 19 to 40 nmol p-nitrophenol released/hour/mg protein. Differences were also found for β -D-glucuronidase (our range, 291 to 376 nmol 4-methylumbelliferone released/hour/mg protein compared to 79 to 251 nmol p-nitrophenol released/hour/mg protein), β-D-hexosaminidase (our range, 1,114 to 2,270 nmol 4-methylumbelliferone released/ hour/mg protein compared to 323 to 719 nmol p-nitrophenol released/hour/mg protein), and α-D-mannosidase (our range, 48 to 158 nmol 4-methylumbelliferone released/hour/mg protein compared to 79 to 359 nmol p-nitrophenol released/hour/mg protein). These differences probably reflect slight variations in assay conditions and different substrates used in the two methods, rather than true differences in enzymatic activities in the leukocytes of the groups studied.

Discussion

We studied lysosomal enzyme activities in serum and leukocytes from 24 patients with

progressive cone dystrophy and ten control subjects. No significant differences were found between the two groups, and no individual patient showed activity significantly below the control range for any enzyme tested. Although six of our patients had similar clinical, electroretinographic, and hereditary characteristics to those of two patients with cone dystrophy reported previously to be partially fucosidase deficient,5 none of our patients were enzyme deficient. It is possible that we could not confirm the previous results because of differences in the genetic makeup of the populations studied. Our patients were predominantly whites from the Pacific Northwest of the United States, whereas the patients in Hayasaka and associates' study were presumably Japanese. We might have found patients with fucosidase deficiency if we had had access to a larger and more heterogeneous group of patients with cone dystrophy. However, it is also possible that the previous observation of low fucosidase activity may have been spurious or coincidental.

Ocular abnormalities, including bull's-eye macular lesions, have been described in patients with fucosidosis who have nearly complete loss of fucosidase activity, but none have ever been reported in obligate carriers. 11,12 Both fucosidase-deficient patients described by Hayasaka and associates had only half the normal level of fucosidase activity. They would therefore be identified as fucosidosis carriers, and no overt ophthalmic symptoms or disease would be expected. Moreover, the carrier state should follow an autosomal dominant pattern of inheritance, whereas Hayasaka and associates' patients both had sporadic inheritance with respect to the retinal disease. Thus, it is not clear that the degree of systemic fucosidase deficiency described in these patients was necessarily related to their cone dystrophy.

Additionally, an isozyme of α -L-fucosidase may be differentially expressed in the retinal pigment epithelium or retina, but not in the serum or leukocytes. Thus, a tissue- or cell-specific defect may still be involved in the origin of a subset of cone dystrophy, but it would not be detected by measuring enzyme activity in serum or leukocytes. Investigation of this possibility would require samples of retinal pigment epithelium for enzyme assay, which is not easily accessible in human subjects. However, such a defect would not explain the findings of Hayasaka and associates.

Fucose does appear to be an important com-

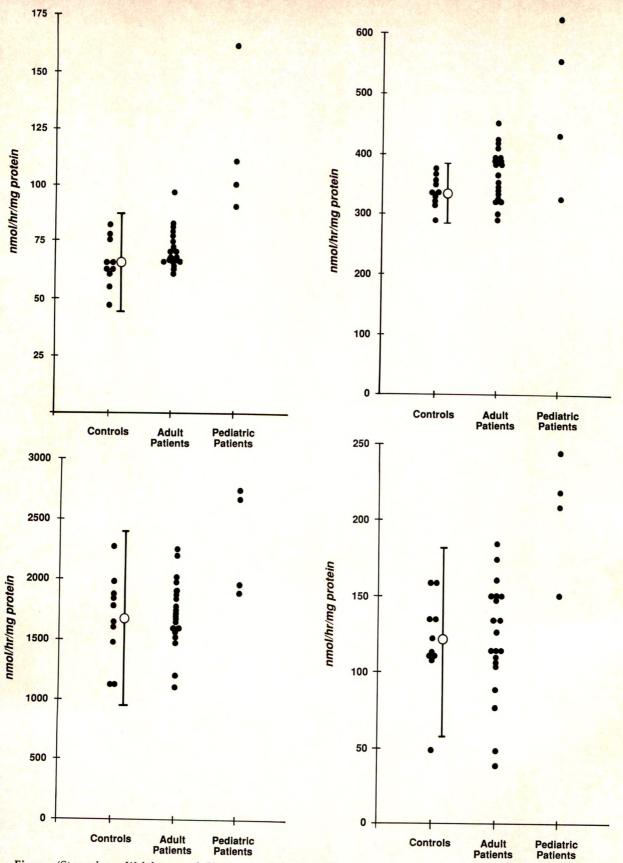


Figure (Stoumbos, Weleber, and Kennaway). Lysosomal enzyme activities in leukocytes. Top left, α-L-Fucosidase; top right, β-D-glucuronidase; bottom left, β-D-hexosaminidase (A + B); bottom right, α-D-mannosidase. Values for normal controls, adult cone dystrophy patients, and pediatric cone dystrophy patients (less than 15 years of age) are shown in separate categories. Solid circles represent mean activity from two to four assays performed on each control or patient sample. Open circles and bars represent mean \pm 2 S.D. for the normal group (see text for actual values of enzymatic activities). For each enzyme studied, the control and patient groups were not statistically different (P > .05), and no patient showed activity significantly below the normal range.

ponent of both rod and cone outer segments. Several studies using radio-labeled fucose have demonstrated that fucose is incorporated by photoreceptors in a wide range of animal species 13,14 as well as humans. 15,16 Fucosylated products include various opsins, interstitial retinol binding protein, and probably several other still unidentified membrane glycoproteins. Although the importance of the fucose moiety itself is not known, these fucosylated products may play a significant role in maintenance of retinal structure and function.17 Similar functions for fucosylated proteins may also exist for cones, although these have been studied less extensively. Since the retinal pigment epithelium is responsible for phagocytosis and digestion of photoreceptor outer segments as well as recycling of interstitial retinol binding protein, it would need a mechanism for degrading the fucosylated compounds. Fucosidase activity has been demonstrated in retinal pigment epithelial preparations from bovine eyes. 18,19 A complete defect of this activity may lead to incomplete degradation of fucosylated glycoproteins, and perhaps damage of the retinal pigment epithelium or the overlying photoreceptors. One could speculate that this may be related to the bull's-eye maculopathy observed in one patient with fucosidosis,12 but it would be unlikely that a partial fucosidase deficiency would cause significant damage. Moreover, since fucosylated glycoproteins are also important in rod function, any damage caused by a fucosidase deficiency would be expected to affect rods as well as cones.

Thus, convincing evidence that systemic fucosidase deficiency is related to any subset of cone dystrophy is still lacking. Localized or tissue-specific fucosidase deficiency, while theoretically possible, would be quite difficult to investigate in humans, and would be unlikely to cause degeneration of cones without affecting rods.

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OPHTHALMIC MINIATURE

I tried to focus my gaze on the water but its movement distracted me. My mind and my eyes began to wander onto other features of the immediate surroundings. Don Juan bobbed my head up and down and ordered me again to gaze only at the water and not think at all. He said it was difficult to stare at the moving water and that one had to keep trying. . . . Finally I noticed that my mind and my eyes were focusing on the water; in spite of its movement I was becoming immersed in my view of its liquidness. . . . And then, suddenly, I had the sensation that I was not looking at a mass of moving water but at a picture of water; what I had in front of my eyes was a frozen segment of the running water.

Carlos Castaneda, A Separate Reality New York, Simon and Schuster, 1971

Uveitis and Diabetes Mellitus

Aniki Rothova, M.D., Christina Meenken, Robert P. J. Michels, M.D., and Aize Kijlstra, Ph.D.

Of 340 patients with anterior uveitis, 20 (6%) had diabetes mellitus. This is significantly higher than the prevalence of 1.4% in the normal Dutch population (P < .001). Of 128 patients with idiopathic anterior uveitis, 16 (12.5%) had diabetes mellitus compared to only four (1.9%) of 212 patients with anterior uveitis with an established specific ocular diagnosis (P < .001). Of the 16 diabetic patients with idiopathic anterior uveitis, ten (63%) had type I diabetes mellitus and 12 (75%) suffered from severe diabetic complications as angiopathy, nephropathy, and neuropathy. The onset of diabetes mellitus preceded the onset of anterior uveitis in all cases. Whether or not uveitis in diabetic patients is a true inflamma tion rather than an ischemic phenomenon is still unknown.

THE ASSOCIATION of uveitis and diabetes mellitus was first described by Noyes1 in a case report more than 100 years ago. This presumed association gained acceptance when, in 1885, nine cases of iritis were found in 36 patients with diabetes mellitus.2 Since then, however, several studies on the frequency of uveitis in diabetes could not confirm the association of uveitis and diabetes mellitus.3-5 In an extensive study of ocular complications in diabetes mellitus, the same frequency of anterior uveitis was reported in diabetic patients and nondiabetic

Wittington and Lawrence proposed that a specific kind of iritis is associated with uncontrolled diabetes mellitus. Guy and associates7 observed iritis in 30% (14 of 47) of insulindependent diabetic patients with severe autonomic neuropathy as compared to 0.7% (one of 143) of control patients (insulin dependent, without autonomic neuropathy).

These studies all dealt with the incidence of uveitis in a population of diabetic patients. We undertook this study to determine the incidence of diabetes mellitus in a population of patients with anterior uveitis. We found a definite association between diabetes mellitus and anterior uveitis.

Material and Methods

We conducted a retrospective analysis of 340 cases of anterior uveitis evaluated by the uveitis clinic of the Academic Medical Centre in Amsterdam between 1982 and 1987. All patients had received an etiologic examination including HLA-B27 typing, serologic tests for syphilis, serum angiotensin converting enzyme, serum lysozyme, and chest x-rays. We used diagnostic criteria for uveitis entities as described by O'Connor.8

All patients were questioned about their medical history, including systemic diseases and medication. The patients' physicians were asked by letter for specific information about the course of the diabetes mellitus (manifestations, treatment, and eventual complications), and we received the information in all cases. Diabetes mellitus type I and type II were defined as described in a World Health Organization report.9 Diagnostic criteria of autonomic symptoms were used as described by Guy and associates.7

We used the chi-square test for statistical analysis. P < .05 was considered significant.

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TABLE 1
SPECIFIC DIAGNOSIS IN PATIENTS WITH
ANTERIOR UVEITIS

	PATIENTS (N = 340)		
DIAGNOSIS	NO.	(%)	
HLA-B27-associated acute anterior uveitis	114	(34)	
Sarcoidosis	19	(6)	
Fuchs' heterochromic cyclitis	19	(6)	
Viral (kerato) uveitis	17	(5)	
Traumatic uveitis	14	(4)	
Juvenile rheumatoid arthritis	6	(2)	
Syphilis	6	(2)	
Tuberculosis	4	(1)	
Glaucomatocyclitic crisis	4	(1)	
Miscellaneous	9	(3)	
No diagnosis established	128	(38)	

Results

The specific diagnosis of anterior uveitis was obtained in 212 of 340 (62%) patients (Table 1). The frequency of diabetes mellitus in patients with anterior uveitis was 6% (20 cases), which is significantly higher than the prevalence of diabetes mellitus in a normal Dutch population (1.4%) (P < .001). Diabetes mellitus was observed in 16 of 128 (12.5%) patients with anterior uveitis in whom a definitive diagnosis could not be determined compared with only

four of 212 (1.9%) anterior uveitis patients with an established diagnosis (P < .001) (Table 2). Of those four diabetic patients, two had HLA-B27-associated acute anterior uveitis, one suffered from biopsy-proven sarcoidosis, and one had herpetic keratouveitis. Of the 20 diabetic patients with anterior uveitis, 12 had diabetes mellitus type I and eight had type II (Table 2). In all diabetic patients with anterior uveitis, the onset of diabetes mellitus preceded the onset of uveitis, with a mean interval of ten years (Table 3).

The clinical picture of anterior uveitis in diabetic patients was not specific. Of 20 diabetic patients with anterior uveitis, 15 (75%) had unilateral ocular involvement and 16 (80%) developed chronic or recurrent anterior uveitis.

The 16 cases of anterior uveitis associated with diabetes mellitus in which a specific ocular diagnosis could not be determined were analyzed thoroughly. Posterior synechiae and cataract were each seen in eight (50%) of these 16 diabetic patients (Table 4). Glaucoma was observed in three of these patients. Seven patients had visual acuity that was 20/200 or less. Associated retinopathy was observed in six patients (38%) and iris neovascularization was noted in two patients (13%). Ten (63%) of the patients had diabetes mellitus type I and six had diabetes mellitus type II (37%) (Table 2). Serious complications of diabetes mellitus were seen in 12 (75%) of these patients (Table 5). In ten of the 12 patients, the autonomic nervous disturbances were present before the onset of anterior uveitis. The interval between the onset of uveitis and autonomic symptoms was less than three years in all cases.

TABLE 2
FREQUENCY OF DIABETES MELLITUS IN PATIENTS WITH ANTERIOR UVEITIS

TYPE OF	ALL PATIENTS (N = 340)		PATIENTS WITH DETERMINED CAUSE (N = 212)		PATIENTS WITH UNDETERMINED CAUSE (N = 128)	
DIABETES MELLITUS	NO.	(%)	NO.	(%)	NO.	(%)
Diabetes mellitus, types I and II	20	(5.8)	4*	(1.9)	16*	(12.5)
Diabetes mellitus, type I	12	(3.5)	2^{\dagger}	(0.9)	10 [†]	(7.8)
Diabetes mellitus, type II	8	(2.3)	2	(0.9)	6	(4.7)

^{*}P < .001.

[†]P < .005.

TABLE 3
CHARACTERISTICS OF DIABETIC PATIENTS WITH
ANTERIOR UVEITIS

CHARACTERISTIC	DIA	US	
	TYPES I AND II	TYPE I	TYPE II
Age at onset of			
diabetes mellitus			
(yrs)	39	33	48
Age at onset of			
anterior uveitis			
(yrs)	49	46	53
Sex ratio, male:female	1:1.7	1:2.3	1:1

Discussion

We found a definite association between diabetes mellitus and anterior uveitis. However, the prevalence of anterior uveitis in the diabetic and nondiabetic population has also been reported to be the same.⁵ Diabetes mellitus, which is a relatively common disease, has an incidence rate of 110:100,000¹⁰ as compared to anterior uveitis, which has an incidence rate of 11:100,000.¹¹ Since anterior uveitis is probably a rare complication of diabetes mellitus, we would not expect an increased frequency in a diabetic population.

Ten (63%) of 16 patients with idiopathic anterior uveitis had diabetes mellitus type I and 12 (75%) suffered from severe diabetic complications including angiopathy, nephropathy, and neuropathy. Six patients (38%) had an autonomic neuropathy, which confirms the previously described association of severe autonom-

TABLE 4

COMPLICATIONS OF IDIOPATHIC ANTERIOR UVEITIS IN
16 PATIENTS WITH DIABETES MELLITUS

	PATIENTS			
COMPLICATIONS	NO.	(%)		
Persisting posterior synechiae	8	(50)		
Cataract	8	(50)		
Glaucoma	3	(19)		
Required surgical intervention	4	(25)		
Visual acuity ≤ 20/200	7	(44)		
Associated retinopathy	6	(38)		
Associated iris neovascularization	2	(13)		

TABLE 5
COMPLICATIONS OF DIABETES MELLITUS IN 16
PATIENTS WITH IDIOPATHIC ANTERIOR UVEITIS

COMPLICATIONS	PATIENTS			
	NO.	(%)		
Cardiopathy	7	(44)		
Neuropathy	6	(38)		
Nephropathy	7	(44)		
Total	12	(75)		

ic neuropathy and anterior uveitis.⁷ These findings suggest that anterior uveitis is associated with diabetes mellitus, characterized by late systemic complications.

Whether or not uveitis in diabetic patients is a true inflammation rather than an ischemic phenomenon is still unknown. The absence of retinopathy in more than half of the diabetic patients with uveitis, recurrent episodes of the disease, and a good response to local corticosteroid therapy suggest an inflammatory process. Nonetheless, focal iris necrosis and subsequent tissue reaction remains a possibility. The interval of ten years between the onset of diabetes mellitus and anterior uveitis is comparable with other late complications of diabetes mellitus.¹²⁻¹⁴ Further investigations, such as iris fluorescein angiography, need to be done to clarify this issue.

Based on this study, we conclude that patients with anterior uveitis also suffering from diabetes mellitus probably have a severe diabetes, frequently complicated by vasculopathy and neuropathy. The high frequency of systemic complications in diabetic patients with anterior uveitis indicates a need for careful monitoring and treatment of their diabetes mellitus.

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OPHTHALMIC MINIATURE

It raises an odd question, in that my right eye has gotten more and more near sighted while my left eye has remained near normal, all occurring since I began heavy use of the sextant, including thousands of day and night horizontal angles. Of course, the use of any telescope removes completely any near sighted problems as the focus is at infinity.

Norman Cubberly, "Readers Forum" in *The Navigator's Newsletter* Foundation for the Promotion of the Art of Navigation, Issue 20, Spring 1988, p. 2

Failure of Preenucleation Radiation to Decrease Uveal Melanoma Mortality

Devron H. Char, M.D., Theodore L. Phillips, M.D., Yvonne Andejeski, M.D., J. Brooks Crawford, M.D., and Stewart Kroll, M.A.

We analyzed uveal melanoma metastases in a group of 41 patients who received 20 Gy of preenucleation radiation in a Northern California Oncology Group preliminary phase I/II study, and compared their survival rates with a retrospective control group of 31 patients with characteristics matching the entrance criteria but treated with enucleation alone. Using the Cox proportional hazards model, we found that increased tumor diameter, mixed or epithelioid cell type, and radiation adversely affected survival. In vivo studies of cell cycling indicated that 20 Gy of preenucleation radiation appeared to diminish the reproductive integrity of the tumor cells. It is most likely that the failure of preenucleation irradiation to prolong patient survival was because of that occurred micrometastases treatment.

WHILE THE OPTIMUM management of large uveal melanomas is uncertain, these tumors have been treated with enucleation alone, perioperative irradiation with enucleation, or different forms of radiation with intent to retain the globe. Possible adverse effects of enucleation trauma have been hypothesized to increase melanoma-related mortality. In some other body sites, perioperative irradiation appears to decrease tumor-related mortality.

Conceivably, if trauma at the time of enucleation was associated with increased tumor mortality, preenucleation radiation might decrease it. In 1977 we initiated a Northern California Oncology Group (NCOG) preliminary phase I/II study of 20 Gy of preenucleation photon irradiation in patients with large uveal melanomas to study some of these issues.³

See also p. 88.

Herein we used a Cox proportional hazards model to analyze retrospectively uveal melanoma metastases after 20 Gy of preenucleation irradiation and observed that this therapy does not favorably affect tumor-related mortality.

Material and Methods

All patients were examined in the Ocular Oncology Unit, University of California, San Francisco, between 1976 and 1985. The diagnosis of a uveal melanoma was established based on multimodality, multiobserver techniques including indirect ophthalmoscopy, fundus photography, fluorescein angiography, and ultrasonography.4 All patients had a complete physical examination before surgery; the metastatic evaluation included a chest x-ray and serum lactic dehydrogenase, alkaline phosphatase, and glutamyl transpeptidase levels. In patients with abnormal physical or laboratory findings, further appropriate metastatic studies including body computed tomography and fine needle aspiration biopsies were performed. No patient had known metastatic disease before treatment.

Patients treated as part of a phase I/II NCOG study of preenucleation irradiation gave both written and oral informed consent before therapy. The criteria for inclusion in the radiation study were a uveal melanoma that was greater than 15 mm in largest diameter or greater than

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From the Ocular Oncology Unit (Drs. Char and Crawford and Mr. Kroll), and the Department of Radiation Oncology (Drs. Char, Phillips, and Andejeski), University of California, San Francisco, and the Northern California Oncology Group. This study was supported in part by an unrestricted grant from That Man May See, National Institutes of Health grants EYO 3675 and EYO 7504, American Cancer Society grant PDT 321, grants from the Beal Foundation and Richard and Gail Siegal, and Public Health Service grants CA-21744 and CA-25827 from the National Cancer Institute.

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5 mm in thickness based on clinical and ultrasound findings, with no evidence of extraocular extension. Tumor size was estimated in all cases on the basis of clinical and ultrasonographic examination. These size measurements were later confirmed on examination of the histologic slides. Histologic parameters were assessed by ocular pathologists without knowledge of the radiation status of the patient.

The treatment group consisted of 41 patients with uveal melanomas of the defined size criteria who had received preenucleation radiation. There were 18 women and 23 men. The mean patient age was 58 years (range, 20 to 86 years) (Table). The mean tumor diameter was 15 mm (range, 7.5 to 22 mm) and the mean tumor thickness was 8.5 mm (range, 3.3 to 17.8 mm). Twenty-eight (68%) of the patients had spindle cell tumors and 13 (32%) had mixed or epithelioid lesions. The tumor location was anterior in 25 cases (61%) and posterior in 16 cases (39%). The mean follow-up was 47 months (range, ten to 83 months); 22 eyes were enucleated over five years ago, and only two were treated within the last three years.

A retrospective control group was chosen from patients whose eyes were enucleated by the same surgeon before the onset of either the phase I/II preenucleation irradiation study or our charged particle helium ion irradiation uveal melanoma treatment trial. The inclusion criteria were otherwise identical (Table). Thirty-one patients were available who qualified on the basis of clinical and ultrasonographic size and absence of known extraocular extension. The mean age in the control group was 58 years. There were 19 women and 12 men. The mean tumor diameter was 14 mm and the mean tumor thickness was 7.3 mm. Mean follow-up time in the control group was 80 months. In contrast to the treatment group, only 11 of the tumors (36%) were spindle cell melanomas, whereas 20 (64%) were mixed or epithelioid lesions. As in the treatment group, the tumor location was anterior in 19 cases (61%) and posterior in 12 cases (39%).

Preenucleation irradiation was performed with a 4-meV linear accelerator using 5×5 -cm anterior and lateral oblique wedge pair ports. Patients received five consecutive daily fractions of 400 cGy radiation for a total of 20 Gy. 3,5 Enucleation was performed in both the treatment and control groups by the same surgeon, using a standard enucleation technique. In the patients who received preenucleation irradia-

TABLE
UVEAL MELANOMA COVARIATES

	TREATED GROUP (N = 41)			CONTROL GROUP (N = 31)				
VARIATE	AVER- AGE	MIN.	MAX.	RANGE	AVER-	MIN.	MAX.	RANGE
Age (yrs) Largest diameter	57.8	20.0	86.0	66.0	57. <mark>6</mark>	16.0	77.0	61.0
(mm) Height of tumor	15.0	7.5	22.0	14.5	13.8	3.0	28.0	25.0
(mm) Months to onset of	8.45	3.3	17.8	14.5	7.10	2.0	14.7	12.7
metastases Months from diagnosis	26.5	7.1	52.4	45.3	57.6	7.6	102.8	95.2
to death	32.2	9.2	59.7	50.5	62.4	11.6	102.8	91.2

tion, enucleation was performed usually within 24 hours but always within 72 hours of completion of radiation.

Complete follow-up through November 1987 was available on all patients. Metastases from uveal melanomas were confirmed in most cases by either open or fine needle aspiration biopsy. In eight cases the diagnosis was established on the basis of a death certificate that demonstrated widespread melanoma. In the treatment group there were 12 deaths (29%) from metastases, and in the control group there were ten (32%).

In a small subgroup of irradiated and nonirradiated uveal melanomas, cell cycling status was studied with in vivo bromodeoxyuridine uptake and tissue culture propagation. These studies were undertaken to analyze the effect of 20 Gy of preenucleation irradiation on the reproductive integrity of the tumor cells. Bromodeoxyuridine is incorporated into cells that are actively cycling. The techniques for bromodeoxyuridine analysis are described in detail elsewhere.6 Briefly, patients were given 200 mg/M2 of bromodeoxyuridine intravenously one hour before surgery. After standard histologic processing of the globe, sections of the tumor were stained with a fluorescent-labeled anti-bromodeoxyuridine antibody, and the number of positive cells in 32 random highpower fields were read in a masked manner by a technician. Tissue culture propagation was

performed in a standard manner. A small piece of tumor tissue was obtained in the operating room and placed in a small tissue culture flask with RPMI 1640 medium with antibiotics and 20% fetal calf serum. Tumor explants were incubated in 5% CO₂ at 37 C. When the adherent monolayer became confluent, the culture was passaged in a standard manner. The number of passages was determined and the end point was either cell death or overgrowth of the tumor cells by fibroblasts.

Statistical analysis was performed using the Cox proportional hazards model and the Student's *t*-test.

Results

Minimal complications were noted after preenucleation irradiation. Two patients developed transient loss of scalp hair at the exit site of the beam. Two other patients had some complaints of a dry socket, and one of these patients had problems wearing a prosthesis.

Metastatic disease occurred in 14 of 41 patients (34%) treated with preenucleation irradiation and 11 of 32 control patients (36%). The onset of metastatic disease occurred significantly sooner in the treatment group; the mean onset of metastases was 26.5 months as compared with 57.6 months in the control group (P < .03). The latency of metastases following surgery was between seven and 103 months. The Figure shows the effect of radiation on the time to the appearance of metastatic melanoma for the control and irradiated groups. The relative hazard of preenculeation radiation for development of metastases, controlling for cell type and tumor diameter, was approximately fivefold (95% confidence interval, two- to twentyfold) as compared to eyes that received no irradiation.

The Cox proportional hazards model was used to study the effect of preenucleation irradiation on metastases, adjusting for other

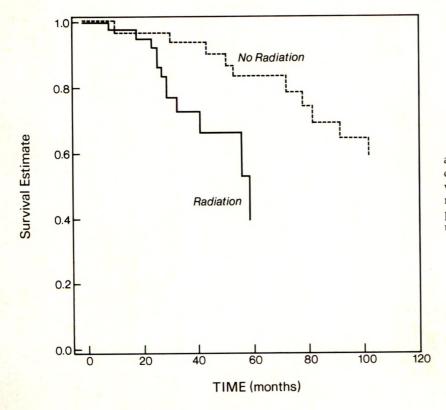


Figure (Char and associates). Kaplan-Meier survival curves demonstrate the adverse effect of 20 Gy of preenucleation irradiation compared with no irradiation on uveal melanoma metastases.

prognostic covariates. The covariates used were age, sex, largest tumor diameter, largest tumor thickness, anterior tumor margin, tumor cell type, and treatment. Development of uveal melanoma metastases was associated with tumors of increased diameter (P < .04) and more malignant cell type (P < .004).

Tissue culture propagation was attempted in seven nonirradiated cases, and all explants grew and could be propagated for three to 15 passages. Conversely, only two of five melanomas that received preenucleation irradiation could be propagated, and the number of cell passages was significantly less (three to seven passages). Similarly, bromodeoxyuridine uptake was significantly less in the irradiated group. In 13 nonirradiated melanomas studied, there were an average of 80 cells in the S-phase in 32 high-power fields. In contrast, five tumors studied after preenucleation radiation demonstrated less than one positive cell in 32 high-power fields (P < .001).

Since there was a discrepancy between cell types in the control and treatment groups, the ocular pathologists were asked to reclassify retrospectively cell type in all cases in a masked manner. They were given a representative section of each case to analyze again in a masked manner. This disparity was again noted on repeat study.

Discussion

The concept of perioperative radiation is not new; in some malignancies the use of 20 Gy of preoperative irradiation has decreased tumor-related mortality. § In this study, we observed minimal morbidity from five 400-cGy fractions of photon irradiation. Unfortunately, preenucleation radiation did not appear to decrease tumor-related mortality. Using Cox proportional hazards analysis, largest tumor diameter, cell type, and radiation were all shown to affect adversely uveal melanoma-related tumor mortality.

The reasons for the poorer prognosis associated with the preenucleation radiation group are unclear. It is possible that more aggressive tumors were selected for preenucleation radiation. While the control group was retrospective, its choice seems reasonable in that the same surgeon used an identical operative technique throughout the study. The control pa-

tients were chosen before the onset of other studies that might have introduced a patient selection bias, and the clinical and ultrasound entrance criteria were virtually identical in both groups (tumor size, location, and patient age). However, there was marked disparity between melanoma cell types and smaller differences in tumor size in the two groups. The anterior location of the tumors was identical. We cannot account for this asymmetry in the control group having more malignant lesions; however, reexamination by ocular pathologists established that this difference was real. The differences in the histologic and size covariates are taken into account in the Cox hazards model analysis. It is doubtful that the difference in cell type was the result of therapy. Little or no tumor necrosis was observed after preenucleation radiation. Similarly, in patients treated with much higher doses of charged particle irradiation we have not observed a significant drift in the tumor cell type.10

In some other studies that are either completed or in progress, similar results have been observed: perioperative radiation did not improve survival. Raivio¹¹ noted no improvement in survival associated with postoperative irradiation in a retrospective analysis of Finnish uveal melanoma data. 11,12 In two ongoing studies of 20 Gy of preenucleation radiation, slightly worse survival has been observed in the irradiated group (James Augsburger, M.D., oral communication). Similarly, in other studies of higher dose postoperative irradiation the effect of treatment on uveal melanoma mortality has been equivocal. 13-16 In some series, slightly better survival has been claimed, while in others the statistical handling of data was unconvincing.14

There are a number of possible explanations to account for the failure of radiation to improve patient survival. It is possible that preenucleation radiation does not adversely affect survival; however, the level of statistical significance makes this unlikely. It is also possible that the Cox multiple regression analysis overadjusted for the more malignant histologic cell type in the control group or failed to account for other unknown factors differing between the two groups, so that radiation may not increase metastases. It is extremely doubtful that preenculeation radiation could improve survival. Furthermore, it is doubtful that either radiation fractionation or dose schedule was suboptimal given the tissue culture and bromodeoxyuridine data, which demonstrated that radiation had significantly altered the reproductive status of the neoplasm. Other investigators have used less sensitive techniques, but have also noted that perioperative irradiation appears to decrease the reproductive integrity of the tumor. ¹⁷⁻¹⁹

It is difficult to develop a satisfactory hypothesis to explain why preenucleation radiation might increase the incidence of metastases. It is not surprising that radiation would not decrease uveal melanoma mortality. Most other tumors that have a beneficial response to radiation have a high rate of local recurrence; that is not the usual course with uveal melanomas. Most likely, micrometastatic disease is present before irradiation and it is not affected by local irradiation of the primary tumor.

Conceivably, low dose radiation could diminish the host-tumor response. Little substantive data exist to support this concept. Jager and associates20 noted that uveal melanomas treated with 8 Gy of preenucleation radiation had less lymphocytic tumor infiltration and fewer tumor cells expressing class II major histocompatibility complex antigens than nonirradiated tumors. Lymphocytic tumor infiltration is not always associated with improved prognosis; therefore, a decrease in intratumor lymphocytes may not have major impact on survival. Probably many instances of class II major histocompatibility complex antigen expression are induced by lymphokines derived from the infiltrating white blood cells. 20,21

ACKNOWLEDGMENT

Richard Juster, Ph.D., and Byron William Brown, Jr., Ph.D., performed confirmational statistical analyses of these data.

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OPHTHALMIC MINIATURE

So the Monks were built with an eye for originality of design and also for practical horse-riding ability. This was important. People, and indeed things, looked more sincere on a horse. So two legs were held to be both more suitable and cheaper than the more normal primes of seventeen, nineteen or twenty-three; the skin the Monks were given was pinkishlooking instead of purple, soft and smooth instead of crenellated. They were also restricted to just the one mouth and nose, but were given instead an additional eye, making for a grand total of two. A strange-looking creature indeed. But truly excellent at believing the most preposterous things.

Douglas Adams, Dirk Gently's Holistic Detective Agency New York, Pocket Books (A Division of Simon and Schuster), 1987, p. 6

Acute Frosted Retinal Periphlebitis

Robert C. Kleiner, M.D., Henry J. Kaplan, M.D., Jeffrey L. Shakin, M.D., Lawrence A. Yannuzzi, M.D., Hal H. Crosswell, Jr., M.D., and Walter C. McLean, Jr., M.D.

We examined three previously healthy young patients who suffered acute visual loss associated with diffuse bilateral retinal periphlebitis. Each patient developed thick, inflammatory infiltrates surrounding all of the retinal veins, creating the appearance of frosted tree branches. Initial visual acuities ranged from 20/20 to hand motions (median, counting fingers). All patients showed rapid improvement after starting oral corticosteroid therapy, and all but one of the six affected eyes regained a visual acuity of 20/20. The clinical appearance and course of these patients matched those of a condition previously described in Japan and labeled frosted branch angiitis. The term "acute frosted retinal periphlebitis" seems to describe more accurately the clinicial findings.

Acute Bilateral retinal vasculitis was described in a 6-year-old boy by Ito and associates¹ in 1976. The development of unusual and thick sheathing surrounding all of the retinal veins prompted the authors to call the condition "frosted branch angiitis." Since that time five similar cases have been reported among children in Japan.²⁻⁵

The clinical features of frosted branch angiitis have been summmarized by Watanabe, Takeda, and Adachi-Usami. Otherwise healthy

patients experience acute bilateral visual disturbance associated with signs of anterior chamber and vitreous inflammation. The fundus appearance is dramatic, with swelling of the retina and severe sheathing of the retinal vessels to the periphery, creating the appearance of frosted branches of a tree. Fluorescein angiography shows late staining and leakage of dye from the vessels, but there is no evidence of decreased blood flow or occlusion. The electroretinograms are reduced in amplitude. No systemic abnormality has been found, and all patients have responded to systemic corticosteroid therapy. In most cases resolution has been accompanied by the appearance of geographic atrophic lesions in the periphery, narrowing of the retinal arteries and veins, and residual hard exudates.

The ages of the patients in the six previously reported cases ranged from 6 to 16 years (median, 9 years). Visual acuity during the acute phase ranged from 20/100 to light perception. Final visual acuity ranged from 20/15 to 20/40.

We studied three additional cases of frosted branch angiitis, all occurring in the United States. The term "acute frosted retinal periphlebitis" is suggested to describe more accurately this condition.

Case Reports

Case 1

A 25-year-old man in good health noted blurred vision in both eyes one week after developing a biopsy-proven scabies rash on his forearms and scrotum. Ocular examination one day after the onset of visual symptoms showed visual acuity of R.E.: 4/200 and L.E.: 20/400. Moderate inflammation was present in the anterior chambers and vitreous of both eyes. Ophthalmoscopy showed extensive white exudates surrounding the retinal veins from the posterior pole to the periphery in both eyes (Fig. 1). No pars plana deposits were present in

Accepted for publication March 9, 1988.

From the Department of Ophthalmology, Emory University (Drs. Kleiner and Kaplan), the Manhattan Eye and Ear Infirmary (Drs. Shakin and Yannuzzi), the Department of Ophthalmology, South Carolina University (Dr. Crosswell), and the Department of Ophthalmology, Duke University (Dr. McLean). Dr. Kleiner was a 1986–1987 Heed Foundation fellow. This study was supported in part by the Macula Foundation (Drs. Shakin and Yannuzzi), and by National Institutes of Health grant EY03723 (Dr. Kaplan).

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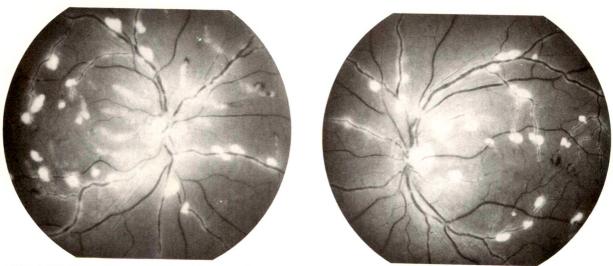


Fig. 1 (Kleiner and associates). Patient 1 at initial examination. Left, Right eye; right, left eye. White exudates surround all of the retinal veins.

either eye. Fluorescein angiography (Fig. 2) showed marked staining of the vein walls of both eyes, but there was no evidence of vascular occlusion or decreased flow.

Four days later the patient's visual acuity had decreased to R.E.: hand motions and L.E.: counting fingers. Ophthalmoscopy showed the perivenous exudates to be increased, with associated widespread intraretinal hemorrhages (Fig. 3). Both retinas were thickened and a

small exudative retinal detachment was present inferiorly in the right eye.

Results of laboratory studies included a normal complete blood cell count and differential, serum electrolytes, erythrocyte sedimentation rate, and lumbar puncture including oligoclonal bands. The serum test for syphilis, tuberculoprotein skin test, human immunodeficiency virus titer, and urine and blood cultures for both bacteria and virus were all negative.

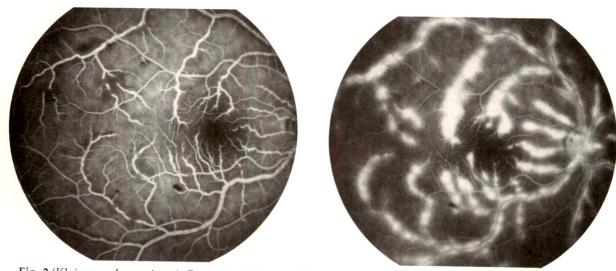


Fig. 2 (Kleiner and associates). Patient 1, right eye, fluorescein angiogram. Left, Early phase; right, late phase. Normal venous flow with late staining of the vein walls.

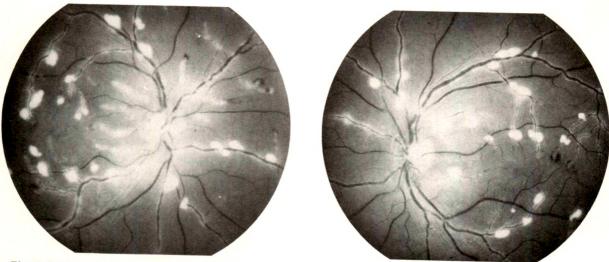


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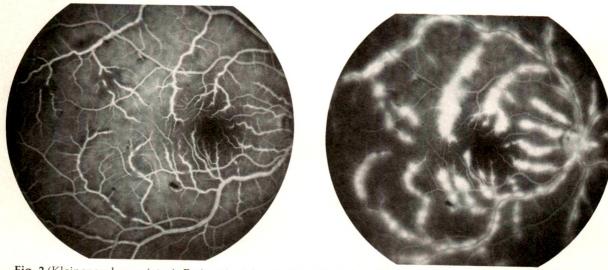


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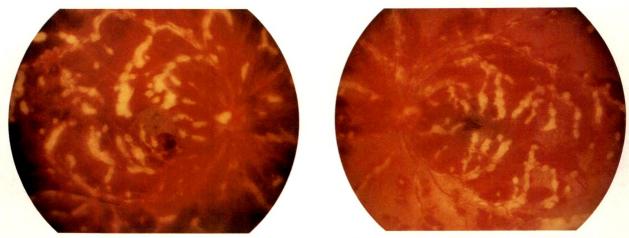


Fig. 3 (Kleiner and associates). Patient 1 four days after initial examination. Left, Right eye; right, left eye. Perivenous exudates are increased and associated with extensive intraretinal hemorrhage.

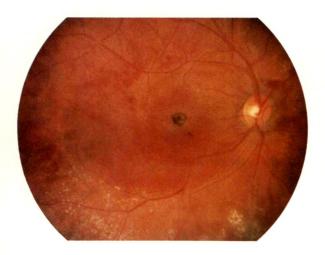


Fig. 4 (Kleiner and associates). Patient 1, right eye, one month after starting oral prednisone. Venous sheathing and hemorrhages are resolving. A small scar is forming in right macula.

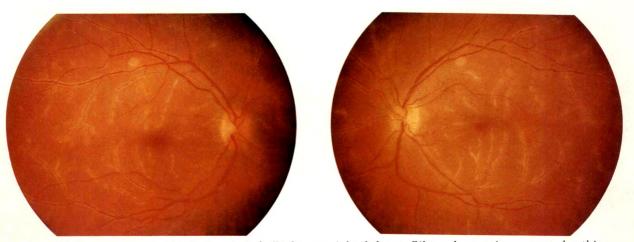


Fig. 5 (Kleiner and associates). Patient 2. Left, Right eye; right, left eye. Bilateral extensive venous sheathing.

Results of chest x-ray, lumbosacral x-rays, and computed tomographic scans of the head and orbits were normal. Serum protein electrophoresis and immunoelectrophoresis were both normal. Antinuclear antibodies were positive at 1:40 with a speckled pattern, a finding reported by the laboratory to be present in many normal individuals.

Four days after the onset of symptoms a regimen was started of topical corticosteroids and 20 mg of oral prednisone four times a day. The vascular sheathing, retinal hemorrhages, and exudative detachment rapidly resolved (Fig. 4), and the corticosteroids were tapered over one month. Four months after initial examination, visual acuity had improved to R.E.: 20/400 and L.E.: 20/80. A small fibrotic scar was present in the macula of the right eye. All of the retinal vessels were attenuated in both eyes, and scattered residual hard exudates were present.

The patient subsequently developed multiple branch vein occlusions in both eyes, prompting another course of oral corticosteroid therapy. In the right eye the vein occlusions were complicated by retinal neovascularization requiring panretinal photocoagulation. Twenty-eight months after initial examination, visual acuity was R.E.: 20/300 and L.E.: 20/20.

Case 2

A previously healthy 29-year-old woman developed decreased vision in both eyes. On examination five days later visual acuity was R.E.: 20/20 and L.E.: 20/30. Moderate cell and flare were present in the anterior chamber and vitreous of both eyes. Ophthalmoscopy showed extensive venous sheathing from the posterior pole to the ora serrata in both eyes (Fig. 5). No pars plana deposits were present. Fluorescein angiography (Fig. 6) showed normal venous filling, with mild late staining of the vein walls.

Results of laboratory studies included a normal complete blood cell count, serum electrolytes, chest x-ray, angiotensin converting enzyme, erythrocyte sedimentation rate, and serum protein electrophoresis. The serum test for syphilis, tuberculoprotein skin test, hepatitis-B surface antigen, and antinuclear antibodies were negative. Serum titers for cytomegalovirus and Epstein-Barr virus were negative; the titer to varicella-zoster was 0.41 (immune, >0.14), to herpes simplex type 1 was 1:160, and to herpes simplex type 2 was 1:320.

Results of a magnetic resonance imaging scan were normal.

Two days after the initial examination the patient received one dose of 40 mg of oral prednisone. The next day visual acuity was R.E.: 20/20 and L.E.: 20/40 and there was marked improvement in the clinical appearance. She was continued on a regimen of oral prednisone, 60 mg/day for ten days, after which her dosage was tapered over six weeks. Ten months after the initial examination, visual acuity was 20/20 in both eyes. A visual field test showed moderate peripheral constriction. No anterior chamber inflammation was present. A few focal areas of venous sheathing remained in the periphery in all quadrants of both eyes, although the posterior pole lesions had resolved (Fig. 7).

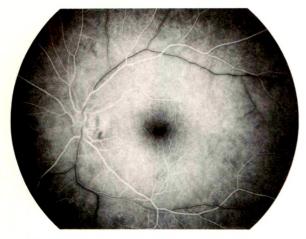
One year after the onset of symptoms the patient developed a posterior vitreous detachment in her left eye with a secondary horseshoe retinal tear in the inferotemporal periphery. This was successfully treated with krypton red laser photocoagulation. The patient has been followed up for six months since that time and has had no additional retinal tears.

Case 3

A 23-year-old woman in good health developed an upper respiratory infection associated with sore throat, fever, and malaise. These symptoms improved spontaneously, but one week later she noted blurred vision in both eyes.

Examination showed visual acuity of counting fingers in both eyes. The pupils reacted sluggishly and an afferent pupillary defect was noted in the left eye. Ophthalmoscopy showed extensive venous sheathing with serous macular detachments in both eyes (Fig. 8). No vitreous cells were noted in either eye.

Results of laboratory studies showed a normal complete blood cell count, erythrocyte sedimentation rate, angiotensin converting enzyme, and chest x-ray. The serum test for syphilis, tuberculoprotein skin test, and lupus erythematosus cell preparation were negative. Results of cerebrospinal fluid examination including protein electrophoresis were normal. Throat cultures showed normal flora. Antistreptolysin O titer was increased at 1:625 Todd units (normal, <1:166 Todd units). A repeat antistreptolysin O titer six days later was 1:133 Todd units. Viral antibody titers were negative in both acute and convalescent serum.



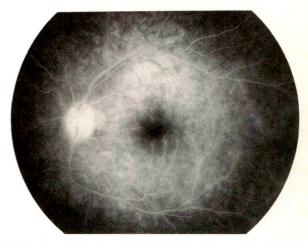


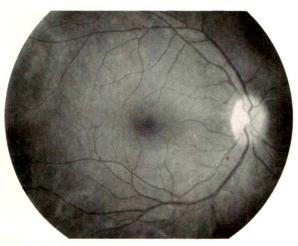
Fig. 6 (Kleiner and associates). Patient 2, left eye, fluorescein angiogram. Left, Transit phase with normal venous flow. Right, Late phase showing mild staining of the vein walls.

The patient was treated with a single intramuscular dose of 6,000 units of penicillin G procaine, followed by 250 mg of oral penicillin V potassium and 25 mg of oral prednisone four times a day. This resulted in improvement of her visual acuity and ophthalmoscopic appearance. The penicillin was continued for ten days while the oral prednisone was continued for two weeks and then tapered over the following two weeks. Three weeks after beginning therapy, visual acuity had improved to 20/30 in both eyes. The venous sheathing had resolved and the macular detachments had flattened, leaving

yellow subretinal deposits in the perimacular region of both eyes. Four months later, visual acuity was 20/20 in both eyes and both fundi appeared normal.

Discussion

All of our otherwise healthy patients described herein developed acute severe retinal periphlebitis characterized by thick, inflammatory infiltrates surrounding all of the retinal



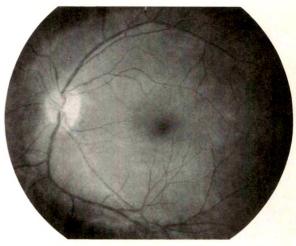


Fig. 7 (Kleiner and associates). Patient 2 ten months after initial examination. Left, Right eye; right, left eye. Venous sheathing has resolved.

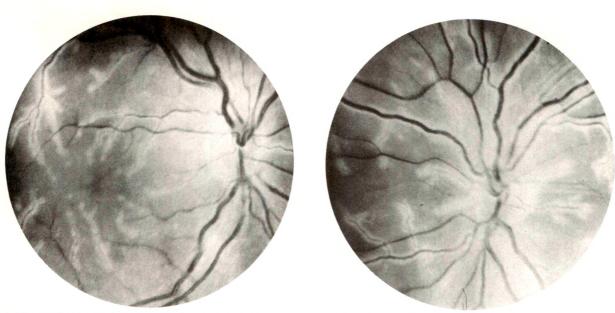


Fig. 8 (Kleiner and associates). Patient 3. Left, Right eye; right, left eye. Extensive venous sheathing is present in both eyes.

veins. Patient 1 also developed diffuse retinal hemorrhages in both eyes and a localized exudative retinal detachment in one eye. Patient 3 developed bilateral macular detachments. All patients showed rapid improvement with resolution of the perivenous infiltrates after starting oral corticosteroid therapy; Patient 3 was also treated with penicillin because of an increased antistreptolysin O titer. Patients 2 and 3 regained visual acuity of 20/20 in both eyes. Patient 1 regained visual acuity of 20/20 in the right eye while the visual acuity in the other eye returned to only 20/300, probably as a result of the development of a fibrous macular scar. While our patients are somewhat older than those previously reported, their clinical course and appearance were similar to those previously described as having frosted branch

Two of our patients developed late complications. Patient 1 developed recurrent bilateral branch vein occlusions requiring the reinstitution of corticosteroid therapy. Patient 2 developed a retinal tear associated with a posterior vitreous detachment. Similar late complications have not previously been reported in association with this syndrome.

The inflammation in the cases reported here involved only the retinal veins. Previous au-

thors have described frosted branch angiitis as affecting all of the retinal vessels. ¹⁻⁵ However, in reviewing four of these reports, we found that two patients ^{1,5} had involvement of only the retinal veins. Three patients had involvement of both arteries and veins, but the veins were more severely affected. ^{2,3} The remaining report was not available for review. ⁴ Thus, it appears that this condition should be considered a primary periphlebitis. Furthermore, the term "frosted branch" is somewhat misleading in that it implies only single branches of the retinal veins are involved. We believe the term "acute frosted retinal periphlebitis" would better describe the clinical course and appearance.

No cause for this condition has been found. Retinal vasculitis affecting predominantly the veins has been reported in association with tuberculosis, ⁶ syphilis, ⁷ sarcoidosis, ⁸ multiple sclerosis, ^{9,10} and human immunodeficiency virus (HIV) infection. ^{11,12} All of our patients had negative test results for tuberculosis and syphilis. Patient 1 had a negative HIV titer. Patients 2 and 3 were not tested. The diagnosis of multiple sclerosis is difficult to exclude with absolute certainty. None of our patients had any neurologic symptoms and Patient 1 had a normal head computed tomographic scan and lumbar puncture including oligoclonal banding. Pa-

tient 2 had a normal magnetic resonance imaging scan. Furthermore, periphlebitic lesions associated with multiple sclerosis have been described as small white perivenous cuffs and inflammatory infiltrates, ¹⁰ rather unlike the thick, widespread perivenous exudates seen in

our patients.

Similarly the diagnosis of sarcoidosis is difficult to exclude, but all patients had normal results on chest x-ray, erythrocyte sedimentation rate, serum calcium, and angiotensin converting enzyme levels. Patient 1 developed a rash one week before the onset of ocular symptoms. This was believed to be compatible with scabies both clinically and on histologic examination. Patient 3 had positive antistreptolysin O titers. The significance of these findings is not known.

Retinal periphlebitis in the absence of any signs of systemic illness can occur in association with peripheral uveitis (pars planitis). ¹³ Patients 1 and 2 had moderate inflammation of the vitreous, but neither had deposits on the pars plana. Periphlebitis associated with peripheral uveitis typically involves predominantly the terminal branches of the retinal veins. Severe diffuse retinal periphlebitis as described here has not been reported in association with peripheral uveitis.

Eales' disease is an uncommon cause of retinal periphlebitis. Although the disease has been associated with tuberculosis, as many as 52% of patients have negative tuberculoprotein skin tests. However, Eales' disease is described as a low-grade retinal phlebitis that produces areas of capillary closure in the periphery, a clinical picture unlike that of the

patients described here.

Patient 2 had isolated positive titers of antibodies to both herpes zoster and herpes simplex. These viruses have been reported in association with retinitis¹⁵⁻¹⁷ and retinal arteritis, ¹⁸ but not with retinal periphlebitis of the type described here. Mild retinal periphlebitis has been described in association with adenovirus infection. ¹⁹ Although the cause of the acute retinal periphlebitis described herein remains unknown, viral infection remains a possibility.

Diffuse acute retinal periphlebitis appears to be a new syndrome that has now occurred in at least three patients in North America. The response of the condition to oral corticosteroids is dramatic and provides an effective means of therapy when this disease is recognized.

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OPHTHALMIC MINIATURE

Living for Sabina meant seeing. Seeing is limited by two borders: strong light, which blinds, and total darkness. Perhaps that was what motivated Sabina's distaste for all extremism. Extremes mean borders beyond which life ends, and a passion for extremism, in art and in politics, is a veiled longing for death.

In Franz the word "light" did not evoke the picture of a landscape basking in the soft glow of day; it evoked the source of light itself: the sun, a light bulb, a spotlight. Franz's associations were familiar metaphors: the sun of righteousness, the lambent flame of the intellect, and so on.

Milan Kundera, The Unbearable Lightness of Being Translated by Michael Henry Hein New York, Harper & Row Publishers, Perennial Library Edition, 1987, p. 94

Ocular Perforation From a Retrobulbar Injection

Mark E. Schneider, M.D., David E. Milstein, M.D., Ray T. Oyakawa, M.D., Richard R. Ober, M.D., and Randy Campo, M.D.

Proliferative vitreoretinopathy occurred in three of seven cases of ocular perforation from retrobulbar injection, resulting in a visual acuity of 20/200 or worse. Direct macular injury and macular pucker occurred in two cases each. Needle injury exit sites were in the posterior pole in all cases. Predisposing factors were not experimentally verified, but associated conditions included axial myopia, multiple injections, traditional superonasal gaze position, previous retinal buckling procedure, and enophthalmos.

Of the nearly one million intraocular lenses implanted during cataract surgery in 1986,¹ almost all were implanted using retrobulbar anesthesia. Additional retrobulbar injections are used before radial keratotomy, vitrectomy, laser procedures, keratoplasty, and strabismus surgeries. Herein we describe seven cases of ocular perforation caused by retrobulbar injection.

Patients and Methods

We reviewed the records of patients seen from 1983 to 1987 by the Vitreoretinal Service of White Memorial Medical Center Department of Ophthalmology. Five cases of ocular perforation from a retrobulbar injection were found. Another two patients had been seen and treated at other institutions by two of us (R.R.O. and R.C.).

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When possible, the type of needle, method of injection, and any details related to the anesthetic injection or the surgery were elicited by direct history from the referring physician.

Case Reports

Case 1

A 65-year-old man was referred for evaluation of ocular perforation in the right eye one day after a canceled cataract operation. The patient had previously undergone scleral buckle surgery in both eyes, with a macular pucker in the right eye. The axial length was 24.80 mm. A retrobulbar injection was given using a sharp, 25-gauge, 1½-inch needle. Several minutes after the injection, the eye seemed unusually soft. Intraocular pressure was 0 mm Hg with a Schiøtz tonometer. Indirect ophthalmoscopy disclosed a sheet of vitreous hemorrhage. The surgery was canceled and the patient was admitted. After bilateral patching, he was put on bed rest.

On examination the next day visual acuity was hand motions at 1 foot, and confrontation visual fields demonstrated a superonasal deficit. No afferent pupillary defect was noted. Intraocular pressure by applanation tonometry was 8 mm Hg in the affected right eye and 12 mm Hg in the left eye. Indirect ophthalmoscopy showed a moderate vitreous hemorrhage and only the peripheral buckle could be visualized. Combined A and B scan ultrasonography demonstrated a retinal detachment. Pars plana vitrectomy, lensectomy, and retinal reattachment procedure were performed with much difficulty because of heavy bleeding. A laceration site superonasal to the optic nerve was identified. After air-fluid exchange, this site was treated with transscleral cryotherapy under the previous scleral buckle. Six days later a supplemental air-fluid exchange was performed and two recent penetration sites were identified inferotemporal and temporal to the fovea. An old penetration site, probably related to the previous retinal detachment surgery, was found inferotemporally. The recent penetration sites were treated with argon laser photocoagulation. Visual acuity improved to 20/100. A second pars plana vitrectomy and retinal reattachment procedure were performed for recurrent detachment caused by proliferative vitreoretinopathy. Visual acuity was 20/200 after reoperation, but recurrent proliferative vitreoretinopathy and vitreous hemorrhage six months postoperatively decreased visual acuity to hand motions.

Case 2

A 72-year-old woman underwent an uneventful cataract extraction in the right eye. The preoperative axial length was 23.5 mm. Intraoperatively, the surgeon noted a poor red reflex. Five days postoperatively, the patient was referred for evaluation of poor vision. On examination visual acuity was light perception. Slit-lamp examination showed 3+ corneal striae. The anterior chamber was deep with 2+ flare and trace cells. Indirect ophthalmoscopy showed a dense vitreous hemorrhage. Ultrasonography demonstrated an inferior retinal detachment. At surgery, an inferior hemorrhagic choroidal detachment and overlying retinal detachment were noted. A linear retinal laceration temporal to the macula was treated with transvitreal cryotherapy and air-fluid exchange. Cryotherapy for 360 degrees of the peripheral retina was performed, followed by placement of an encircling scleral buckle. Postoperatively, visual acuity improved to 20/200. Subsequent development of proliferative vitreoretinopathy and contraction of preretinal membranes temporal to the retinal laceration produced traction retinal detachment of the inferior 180 degrees. A pars plana vitrectomy with membrane peeling was unsuccessful in removing the membranes. Visual acuity was hand motions one month after the second procedure.

Case 3

A 78-year-old woman was referred for evaluation of vitreous hemorrhage six weeks after cataract extraction in the left eye. The preoperative axial length was 21.43 mm. A 23-gauge, nondisposable, Atkinson needle had been used, and multiple injections were needed to produce akinesia and anesthesia. A mild, non-progressive retrobulbar hemorrhage occurred. The cataract extraction was complicated by subluxation of the lens and vitreous loss. An ante-

rior vitrectomy was performed and an intraocular lens was not implanted.

On examination visual acuity was hand motions in the left eye, and markedly deep-set eyes were noted. The anterior segment was remarkable for corneal striae, moderate ray and cell with pigment, blood, and capsular remnants. Intraocular pressure by applanation tonometry was 27 mm Hg. Ophthalmoscopy demonstrated a moderate vitreous hemorrhage and retinal detachment with stage C2 proliferative vitreoretinopathy.2 A pars plana vitrectomy and retinal reattachment procedure were performed. At surgery, seven penetration sites were found around the macula, which caused partial adherence of the macula in those areas. Postoperative visual acuity was 20/400, but proliferative vitreoretinopathy caused a recurrent detachment. Final visual acuity was light perception. No further surgery was recommended.

Case 4

A 66-year-old woman was referred one day after an uneventful cataract extraction for evaluation of vitreous hemorrhage in the right eye. Visual acuity was hand motions. The preoperative axial length was 28.46 mm. Slit-lamp examination showed 2+ flare and cell in the anterior chamber, with an intact posterior capsule and no intraocular lens. Ophthalmoscopy showed moderate vitreous hemorrhage, primarily in the posterior pole. The retina was attached peripherally. Ultrasonography showed no retinal detachment. A pars plana vitrectomy was performed nine days later because of decreased visual acuity to light perception and development of an afferent pupillary defect. A linear scar nasal to the disk and a small round pinpoint scar with mild pigmentary changes inferotemporally to the macula were noted. These were believed to represent ocular perforation and they were not treated. One year after surgery, the retina was attached and best corrected visual acuity was 20/40.

Case 5

A 76-year-old woman was referred for evaluation of vitreous hemorrhage three days after cataract extraction in the left eye. Visual acuity was counting fingers. The preoperative axial length was 22.14 mm. The surgeon had used a standard Atkinson technique with a blunt 23-gauge needle. Because of inadequate anesthesia, the injection was repeated twice, using a sharp, 25-gauge, 1½-inch needle. After the

injection, the surgeon noted hypotony but a good red reflex. A posterior chamber intraocular lens was implanted without difficulty. A vitreous hemorrhage noted on the first postoperative day prompted referral to one of us (R.R.O.).

External examination showed mild periorbital ecchymosis. A moderate vitreous hemorrhage obscured the disk and macula and a bullous retinal detachment was present superiorly. A pars plana vitrectomy was performed. At surgery, an irregular retinal tear, 1 disk diameter in size, was noted 3 disk diameters superonasal to the optic nerve in detached retina. Another small tear was noted below the inferotemporal arcade about 3 disk diameters from the nerve head in attached retina. Endodrainage and fluid-gas exchange using 30% sulfahexafluoride were performed. The superior tear was treated with transscleral cryothermy. Six months postoperatively, visual acuity was 20/30, with a small amount of epiretinal fibrosis inferior to the macula.

Case 6

A 48-year-old man was referred for evaluation of poor vision in the right eye following radial keratotomy. The patient initially underwent radial keratotomy in May 1986, and a repeat radial keratotomy was performed in November 1986. Preoperative axial length was 26.83 mm. Before the second procedure, retrobulbar injection was performed using a 27-gauge, sharp, 1¼-inch needle. The patient was noted to have been moving at the time of injection. One day after surgery, the patient noted decreased vision and a central scotoma.

On examination, best corrected visual acuity was 20/200. Ophthalmoscopy disclosed a linear scar just inferior to the macula showing bare sclera. In the inferotemporal periphery, a pinpoint white hypopigmented area and an old vitreous hemorrhage were seen. Contact lens examination of the macula demonstrated a round, full-thickness hole next to the fovea. Visual acuity remained stable at 20/200 after two months of follow-up.

Case 7

A 75-year-old man had undergone an uneventful cataract extraction with placement of an iris clip lens to the left eye. Preoperative axial length was 23.76 mm. The left eye developed cystoid macular edema five months postoperatively, and the patient was referred for examination and treatment. Best corrected vis-

ual acuity was 20/400. Retrobulbar corticosteroid injection was attempted inferotemporally with a sharp, 27-gauge, 11/4-needle. The corticosteroid was not injected because resistance to the tip of the needle resulted in a "poking through sensation." The fundus was examined immediately and a double penetrating tract was seen entering inferiorly and exiting below the macula. Vitreous hemorrhage was also present. Laser photocoagulation was immediately placed around both penetration sites. Additional vitreous hemorrhage developed over the next week without retinal detachment. Six months later, the vitreous hemorrhage had cleared, but significant preretinal macular fibrosis had developed. One year later, subretinal neovascularization developed at the injury site and visual acuity was stable at 20/200.

Results

Seven cases of ocular perforation followed retrobulbar anesthesia, five of which occurred before cataract extraction, one occurred before radial keratotomy, and one case was the result of attempted corticosteroid retrobulbar injection. Sharp, disposable, 25- or 27-gauge, 11/4- or 1½-inch needles were used in six cases. In one case, a 23-gauge Atkinson nondisposable needle was used. Clinical signs associated with ocular perforation included hypotony (Cases 1 and 5), poor red reflex (Case 2), retrobulbar hemorrhage (Case 3), "poking through sensation" (Case 7), and vitreous hemorrhage (all cases). Cases 1, 4, and 6 were associated with axial myopia.3 Patients 3 and 5 received multiple injections. Patient 1 had a previously placed scleral buckle and Patient 3 had deep-set eyes. In Cases 2 and 5 no associated factors could be found. The time interval from perforation to referral ranged from one day to two months. Four cases were referred within the first day, two within the first two weeks, and one within two months after the perforation.

Final visual acuity was hand motions in three patients, largely because of recurrent detachment caused by proliferative vitreoretinopathy. One patient had a visual acuity of 20/200 because of macular pucker; however, visual acuity had been 20/400 before perforation secondary to cystoid macular edema. One patient had a visual acuity of 20/200 as a result of direct macular injury. Two patients had a visual acuity of 20/40 or better.

Five eyes underwent surgical intervention, one patient received argon laser photocoagulation to the perforation sites, and one patient had no treatment. Entrance sites of the perforation clustered around the inferotemporal equator and exit sites were usually located in the posterior pole (Figs. 1 and 2).

Discussion

Complications from retrobulbar injection, including closure of the central retinal artery, contralateral amaurosis, blindness secondary to optic nerve damage, respiratory arrest, and globe perforation, are being reported with increasing frequency. Reports of globe perforation following retrobulbar needle anesthesia are infrequent.

In 1962, Rosen⁹ mentioned globe perforation in association with severe myopia and posterior staphyloma. Cibas¹⁰ described one case of globe perforation by injection needle in his series of 1,000 patients undergoing retinal detachment surgery. Schlaegal and Wilson¹¹ described six cases of intraocular corticosteroid injection, two from standard inferotemporal retrobulbar injection and four from superotemporal retrobulbar injection. Ramsay and Knobloch¹² de-

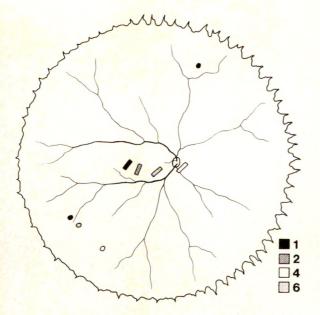


Fig. 1 (Schneider and associates). Right eye. Key denotes entry and exit sites by case number.

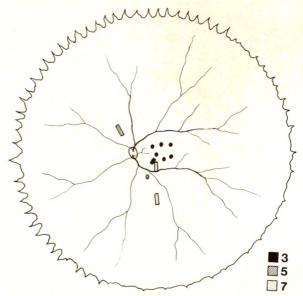


Fig. 2 (Schneider and associates). Left eye. Key denotes entry and exit sites by case number.

scribed three cases of ocular perforation from an injection needle in their series of 4,000 patients.

Predisposing factors to globe perforation may exist. Increased axial length and multiple injections have been implicated by Ramsay and Knobloch. 12 Rosen also hypothesized that scleral thinning from posterior staphyloma and increased axial length may be significant predisposing factors. Kiernan, Leveille, and Morse¹³ demonstrated that retinal buckling results in variable axial length changes, although usually not more than 1 or 2 mm. In these patients, intraconal injection may be technically difficult. All of the perforations seen in our cases were associated with the use of an injection technique similar to that described by Atkinson. 14-16 He advocated the use of a 22gauge, 3.5-cm, blunt needle, and began the injection at the junction of the outer and middle one third of the infraorbital rim while he directed the patients to gaze superonasally. The needle is directed upward and inward, midway between the lateral and inferior recti muscles, and advanced toward the apex of the orbit.

In 1981 Unsold, Stanley, and DeGroot¹⁷ by using computed tomography demonstrated macula and optic nerve vulnerability in a cadaver undergoing Atkinson's approach to retrobulbar injection. Our observations correlate

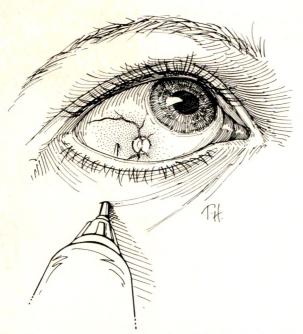


Fig. 3 (Schneider and associates). Optic nerve and macula vulnerability to perforation when classic Atkinson gaze position is utilized.

well with theirs as well as those of Ramsay and Knobloch, 12 since our seven patients all had perforations involving the posterior pole.

Given the potential risk to the macula and optic nerve from the superotemporal gaze position (Fig. 3), it has been suggested that the patient should look straight ahead or slightly inferotemporally during the injection. 17 Variations in technique and gaze position during intraconal injection may avoid some of the complications of the traditional Atkinson technique, yet the need for intraconal anesthesia is increasingly questioned. Various alternative techniques including extraconal retrobulbar18 and peribulbar anesthesia 19,20 have been described, each with stated advantages over the traditional Atkinson technique. Although these techniques seem promising, a recent case of globe perforation after peribulbar anesthesia has been reported.21

While local anesthesia remains the method of choice for most ophthalmic procedures, general anesthesia might be considered for patients with significant enophthalmos, severe myopia, or a scleral buckle. When retrobulbar anesthesia is given, a modified intraconal technique or an extratenons peribulbar injection may prove safer than traditional methods. One of us

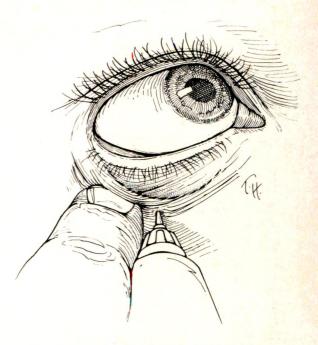


Fig. 4 (Schneider and associates). Index finger elevating globe during insertion of retrobulbar needle.

(R.T.O.) uses a technique of elevating the globe with an index finger as a modification to the Atkinson technique (Fig. 4).

Proliferative vitreoretinopathy developed in three of our seven patients, resulting in a visual acuity of less than 20/200. Macular pucker occurred in two of seven patients. The development of proliferative vitreoretinopathy after double penetrating injury by the retrobulbar needle correlates with the findings of Cleary and Ryan22 in an animal model. In this model a double penetrating injury is produced, followed by injection of autologous blood through the penetration site. In none of our cases did we observe a tract as described by Cleary and Ryan²² or Topping, Abrams, and Machemer.²³ Factors such as the presence of posterior vitreous detachment, which is commonly seen in this age group,24 and the use of a small surgical needle may militate against formation of a

Cleary and Ryan²⁵ demonstrated in the animal model that the ideal time for surgical intervention after double penetrating injury was approximately ten days. By 70 days, most of the animal eyes were inoperable. Therefore, we believe that a careful ophthalmoscopic examination should be performed within ten days in

all patients in which retrobulbar anesthesia was used.

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OPHTHALMIC MINIATURE

But if ye saw that which no eyes can see, The inward beauty of her lively spright, Garnisht with heavenly guifts of high degree, Much more than would ye wonder at that sight, And stand astonisht lyke to those which red Medusaes mazeful hed.

Edmund Spenser, "Epithalamion," 1595

Management of Anterior Chamber Depth After Trabeculectomy

William C. Stewart, M.D., and M. Bruce Shields, M.D.

We followed up 36 eyes of 34 patients for the first three months after trabeculectomy, paying special attention to the depth of the anterior chamber. A significant difference in postoperative course was noted between those eyes with central cornea-lens touch and those with cornea-iris touch but no contact between cornea and lens. The former group (four eyes) had a high rate of complications, including corneal edema, cataract, and bleb failure, despite early efforts to reform the anterior chamber. The latter group (18 eyes), in which the anterior chambers were all allowed to reform spontaneously, had a favorable course, similar to those eyes that maintained formed anterior chambers throughout the study.

A FLAT ANTERIOR CHAMBER is a common early postoperative complication of glaucoma filtering surgery. Serious sequelae of this complication include corneal edema, cataract formation, and bleb failure. Surgeons have, therefore, devised modifications of the filtering procedure to minimize the postoperative flat chamber and usually take additional measures to reform the chamber when the complication does occur. 1-5

The timing of the intervention to reform the anterior chamber after filtering surgery differs from surgeon to surgeon. Some intervene only in cases with central cornea-lens touch, while others also reform chambers with peripheral cornea-iris touch but no central contact between cornea and lens. Since treatment of the flat anterior chamber has the potential for creating additional complications, including failure of the filtering procedure, it is important to decide when and when not to intervene.

We studied the short-term postoperative

course of a consecutive series of patients who underwent trabeculectomy in which conservative management was used for those with cornea-iris touch but no central cornea-lens contact.

Material and Methods

The study population was a consecutive group of adult patients who underwent trabeculectomy for glaucoma that was uncontrolled despite maximum tolerable medical and laser therapy. All surgery was performed by us at the Duke University Eye Center over a tenmonth period. Criteria for exclusion were aphakia, pseudophakia, and filtering surgery combined with cataract extraction.

The basic surgical technique, which was used in all cases, began with a limbal stab incision in the inferotemporal quadrant in order to inject balanced salt solution into the anterior chamber at the end of the procedure. A limbal-based conjunctival flap was prepared by incising conjunctiva for two to three clock hours, 6 to 8 mm behind the corneoscleral limbus, and dissecting between conjunctiva and Tenon's capsule down to the corneoscleral limbus. Underlying Tenon's capsule was then dissected from epihalf-thickness, A and excised. sclera triangular-shaped scleral flap measuring approximately 4 × 4 mm was prepared, and a 2 × 3-mm section of deep limbal tissue was exised from beneath the base of the triangular flap. A peripheral iridectomy was then made beneath the fistula. The scleral flap was approximated with a single 10-0 nylon suture at the posterior apex, and the conjunctival incision was closed with a tight running suture of 10-0 polyglycolic acid. Balanced salt solution was then injected into the anterior chamber to deepen the chamber and elevate the conjunctival flap. Watertight closure was determined by direct inspection for wound leaks and by observing that the conjunctival bleb did not collapse. Additional

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conjunctival sutures were used to close all leaks. The eye was dressed with atropine and an antibiotic-corticosteroid ointment at the end of the procedure.

The patients were examined on the first and second day after surgery and then at postoperative weeks 1, 2, 4, 8, and 12, with more frequent visits as required. Each examination included documentation of visual acuity, intraocular pressure, inflammatory changes, appearance of the filtering bleb, depth of the anterior chamber, patency of the peripheral iridectomy, and the status of the cornea, lens, retina, and optic nerve head. The topical atropine was continued for two weeks and the antibiotic-corticosteroid combination for at least four weeks.

For purposes of this study, the following classification scheme was devised for anterior chamber depth (Fig. 1). In Grade 1, the peripheral anterior chamber depth is equal to or greater than one-quarter corneal thickness. In Grade 2, the peripheral anterior chamber depth is slit-like, measuring less than one-quarter corneal thickness, but there is no evidence of touch between the cornea and the iris or lens. In Grade 3, cornea-iris touch is present. However, the contact between cornea and iris is gentle, with no flattening of the iris stroma, and the cornea is well away from the lens and is not edematous (Fig. 2). In Grade 4, there is central contact between cornea and lens, which is nearly always associated with flattening of the iris stroma and edema of the cornea.

When Grade 3 or Grade 4 anterior chamber depth was found at any time during the postoperative follow-up period, an attempt was made to discover the cause, such as a wound leak or choroidal detachment. When a specific cause was detected, corrective measures were taken in all cases. When no cause for a Grade 4 chamber was determined, it was assumed to be caused by excessive filtration, and the eye was treated with pressure patching. This consisted of placing a fusiform-shaped cotton tamponade over the upper eyelid in the quadrant of the filtering bleb, covering this with two gauze pads, and taping tightly. The pressure patch was left in place for three to four hours, during which time the patient was instructed to stay awake and look straight ahead with the fellow eye to keep the tamponade over the filtering bleb. If a Grade 4 chamber persisted after repeated patching, usually for two days, the anterior chamber was reformed with air or a viscoelastic substance. If no specific cause was

found for a Grade 3 chamber, these eyes were followed up without patching or any other special intervention.

Results

Thirty-six eyes of 34 patients were included in the study. The patients ranged in age from 19 to 83 years (average, 62.4 years). Twenty-eight were white and six were black, and there were 18 men and 16 women. The diagnosis was primary open-angle glaucoma in 26 patients, neovascular glaucoma in four, iridocorneal endothelial syndrome with secondary glaucoma in two, low-tension glaucoma in one, and aniridia with secondary glaucoma in one.

Fourteen of the 36 eyes maintained a Grade 1 or Grade 2 anterior chamber depth throughout the study, with most of these progressing from a Grade 2 to a Grade 1 chamber depth during the first several postoperative weeks. Eighteen eyes had a Grade 3 chamber depth during the early postoperative course, whereas four eyes of four patients had a Grade 4 chamber depth within the first few weeks after surgery.

Of the four patients with a Grade 4 chamber, three had primary open-angle glaucoma and one had glaucoma associated with aniridia. Two of the patients with open-angle glaucoma had large choroidal detachments and hypotony and the third was found to have a wound leak at the third postoperative week. No specific cause for the flat anterior chamber was detected in the patient with aniridia.

The two patients with choroidal detachments were treated with drainage of the detachments. In one patient this resulted in permanent reformation of the anterior chamber, but the other patient developed an intumescent lens and malignant glaucoma. The patient with a wound leak was treated with surgical closure of the defect, resulting in a deep anterior chamber. The patient with aniridia was treated with pressure patching, which led to permanent reformation of the anterior chamber.

Although the primary intervention to correct the flat anterior chamber was successful in three of the four patients, the filtering bleb was lost in all cases, requiring further surgical intervention to control the intraocular pressure. The flat anterior chamber was associated with corneal edema in all four patients, and it persisted in the patient who developed malignant glaucoma.

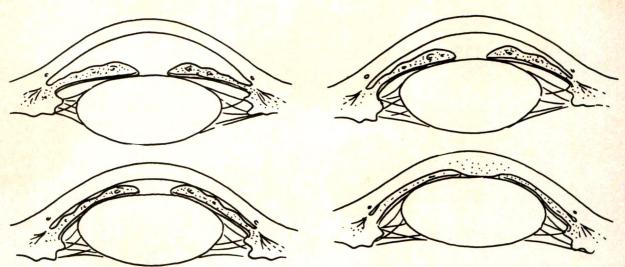


Fig. 1 (Stewart and Shields). Classification scheme used for grading anterior chamber depth in present study. Top left, Grade 1. The peripheral anterior chamber depth is equal to or greater than one-quarter corneal thickness. Top right, Grade 2. The peripheral anterior chamber depth is slit-like, measuring less than one-quarter corneal thickness, but there is no contact between the cornea and the iris or lens. Bottom left, Grade 3. There is cornea-iris touch, but no cornea-lens contact. The iris stroma is not flattened and the cornea is not edematous. Bottom right, Grade 4. There is cornea-lens touch, usually associated with flattening of the iris stroma and edema of the cornea.



Fig. 2 (Stewart and Shields). Slit-lamp view of an eye with a typical Grade 3 anterior chamber depth during the early postoperative period after trabeculectomy. There is gentle, cornea-iris touch, without compression of the iris stroma. The central cornea and lens are well separated and there is no corneal edema.

Of the 18 eyes classified as Grade 3, none were found to have a specific cause for the shallowness of the anterior chamber and all deepened to Grade 1 without additional intervention. The time required for spontaneous deepening of the anterior chamber was one week in nine cases, two weeks in seven, and three weeks in two. The only sequelae noted in association with this gradual reformation of the anterior chamber were anterior synechiae, usually adjacent to the peripheral iridectomy or the limbal stab incision. These synechiae did not seem to have an adverse effect on the outcome of the procedure.

By the third postoperative month, 15 (84%) of the 18 eyes with an initial Grade 3 chamber depth had intraocular pressures of 17 mm Hg or less, and 12 (86%) of the 14 eyes that maintained a Grade 1 or Grade 2 chamber depth throughout the study had final pressures of 17 mm Hg or less. The difference in threemonth pressure control between these two groups was not statistically significant (P > .05).

Of the three eyes with Grade 3 chambers in which intraocular pressure was not adequately controlled after the first filtering procedure, one was subsequently controlled with excision of a Tenon's cyst, one with a repeat filtering operation, and one with cyclocryotherapy. Of

the two eyes with Grade 1 or Grade 2 chambers with inadequate control of intraocular pressure after the initial procedure, one was controlled with revision of the filtering bleb and one with excision of a Tenon's cyst.

Discussion

We undertook this study to evaluate a conservative approach to the management of Grade 3 depth anterior chambers after trabeculectomy. Previous experience by one of us (M.B.S.) led to the observation that early intervention to deepen the anterior chambers in such cases, usually by pressure patching, was often associated with a reduced function, or occasional loss, of the filtering bleb. A valid criticism of the study is the lack of a control group of patients who were randomized to undergo intervention to reform Grade 3 chambers. Rather than comparing the conservative approach to early intervention in these cases, however, we sought to compare the early postoperative course of patients who received conservative management for Grade 3 anterior chambers to that of patients with Grades 1, 2, and 4 postoperative anterior chambers.

We found a clinically significant difference between eyes with Grade 4 and Grade 3 postoperative anterior chambers. The former eyes usually had associated corneal edema and a specific cause for the flat chamber, which may have been a serous or hemorrhagic choroidal detachment, a wound leak, an intumescent lens, or malignant glaucoma. All eyes with Grade 4 chambers require prompt intervention to correct the specific cause of the flat chamber or to reform the chamber by pressure patching or injections into the anterior chamber when a specific cause is not detected. Unfortunately, most of these patients will lose their filtering blebs during the course of trying to reform the chamber, and some will develop cataracts and permanent corneal edema.

In contrast to patients with Grade 4 chambers, those with Grade 3 depth chambers rarely developed corneal edema or other significant complications and nearly always spontaneously regained a deep anterior chamber within days or weeks after the filtering surgery. A Grade 3 chamber probably occurs from early, excessive filtration caused by an initially oversized bleb. As the eye heals and the bleb decreases in size, filtration lessens and the anterior chamber deepens. Reduced aqueous

humor production, secondary to postoperative inflammation, may be another cause for an early shallow anterior chamber. It seems that cornea-lens touch is usually required for corneal decompensation. The iris may act as a buffer between the cornea and lens. Eyes with aniridia appeared to be especially prone to developing Grade 4 anterior chambers in the early post-filtering period, possibly because of the lack of iris between cornea and lens.

Eyes with Grade 3 chambers, which were allowed to deepen spontaneously, followed an early postoperative course similar to that of eyes that maintained a Grade 1 or Grade 2 depth throughout the study. Intraocular pressure control was not statistically significantly different between these two groups three months after surgery, and the only difference in complications was more anterior synechiae in the former group, which did not appear to be functionally significant. Since attempts to accelerate deepening of Grade 3 chambers with pressure patching may compromise the longterm survival of the filtering bleb by limiting aqueous humor filtration and promoting bleb scarring, it is currently our practice to manage these eyes conservatively, as described in this study. However, this study provides only the short-term postoperative results. We are continuing to examine these patients to see if the gradual, spontaneous reformation of Grade 3 chambers has any adverse effect on the longterm results, as compared to eyes that maintained Grade 1 or Grade 2 anterior chamber depths throughout the early postoperative period.

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The Effect of Omitting Botulinum Toxin From the Lower Eyelid in Blepharospasm Treatment

Bartley R. Frueh, M.D., Christine C. Nelson, M.D., James F. Kapustiak, M.D., and David C. Musch, Ph.D.

We randomly selected 26 patients with essential blepharospasm to receive either botulinum toxin or saline injection in their lower eyelids to evaluate the necessity of lower eyelid injection to relieve blepharospasm. As diplopia may occur from botulinum toxin injections for blepharospasm, most commonly from injection of the lower eyelid, and surgical relief of blepharospasm is often achieved by excision of only the upper eyelid protractors, omission of toxin from the lower eyelid seemed both desirable and possible. All patients received botulinum toxin in the upper eyelids, above the eyebrows, across the glabella, and near the lateral canthus. Thirteen of 15 patients who received saline in their lower eyelids had relief of spasm, with the same spasm-free interval as those who received toxin. We recommend avoiding injection of toxin in the medial two thirds of the lower eyelid in order to diminish the likelihood of diplopia from inferior oblique muscle paresis.

THE TREATMENT OF facial spasm with botulinum toxin has become an accepted therapeutic modality, ¹⁻⁷ although the procedure is approved by the Food and Drug Administration only on an experimental basis. While the toxin effectively induces a period of spasm relief, some patients experience diplopia as a side effect of botulinum toxin injection. A recent study found that most cases of diplopia after

botulinum toxin injection were the result of lower eyelid injection affecting the inferior oblique muscle. Because many patients with blepharospasm are free of spasm after extirpation of only the upper eyelid protractors, so the role of the lower eyelid protractors in blepharospasm is not clear. We therefore studied the effectiveness of injecting botulinum toxin in the upper eyelid and brow areas alone vs both upper and lower eyelids for relief of blepharospasm.

Patients and Methods

We randomly assigned 26 patients with essential blepharospasm who desired botulinum toxin treatment to receive either botulinum toxin or saline injection in their lower eyelids, while receiving botulinum toxin in the upper eyelids, above the eyebrows, across the glabella, and around the lateral canthus. Patients were recruited for this study between December 1985 and April 1986, when our supply of botulinum toxin was exhausted and no further toxin was available.

The study included five patients who were receiving botulinum toxin for the first time and 21 who had previously been successfully treated with it. The median number of previous treatments with botulinum toxin injections given to this latter group was two (range, one to ten).

Based on randomized assignment prepared from a table of random numbers, a technician prepared two syringes, one for the lower eyelid, which contained either toxin or saline, and one with toxin for the remainder of the injection. Neither the treating physician nor the patient knew whether the syringe for the lower eyelids contained botulinum toxin or saline. Of the 26 patients studied, 15 received saline and 11 received botulinum toxin in their lower eyelids.

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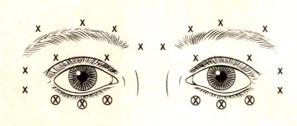
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Each patient received a total of 43 units of botulinum toxin distributed to the upper eyelids, above the eyebrows, the glabellar area, and the lateral canthal area in doses of 2.5 units in 0.05 ml of saline distributed in the configuration shown in the Figure. Each lower eyelid received either three separate injections of 2.5 units of toxin in 0.05 ml of saline or three aliquots of 0.05 ml of saline. All patients returned two weeks after the initial injection and were asked whether their spasm was relieved and if they had experienced any double vision. An ophthalmic examination was performed to determine ocular alignment and detect signs of spasm. For patients who had not received sufficient relief from the spasm, the code was broken and toxin injections to the lower eyelids were administered if they had not initially received toxin.

Each patient was instructed to contact the clinic when the spasm had returned sufficiently to be distressing. The spasm-free interval was based on the time from injection to the patient-initiated report of intolerable spasm recurrence.

Results

Of the 15 patients receiving saline injections in the lower eyelids, two (13%) had insufficient relief of spasm. Each of these patients required a lower eyelid injection of toxin at their two-week follow-up visit. Both were relieved of their spasms after the lower eyelid injection of



X = 2.5U Botulinum Toxin in 0.05cc



Figure (Frueh and associates). The injection sites used in this study for 0.05-ml aliquots containing 2.5 units of botulinum toxin solution and the masked solution, which contained either botulinum toxin or saline.

botulinum toxin had been administered. All 11 patients receiving botulinum toxin in their lower eyelids had relief of their spasms.

The spasm-free interval after injection was 10.5 weeks (S.D. = 3.9 weeks) for the patients receiving both upper and lower injections of botulinum toxin, and 11.8 weeks (S.D. = 4.6 weeks) for the patients receiving saline in their lower eyelids (Table 1). There was no significant difference in the spasm-free interval between the two groups (Student's t-test, P > .30).

Two patients who received botulinum toxin in the lower eyelids (18%) developed diplopia (Table 2). Each had undergone multiple series of injections previously, and had experienced diplopia from the lower eyelid injections after most of the injections. None of the 15 patients receiving saline experienced diplopia. However, there was no significant difference in incidence of diplopia between the groups by Fisher's exact test (P = .17).

Discussion

The use of botulinum toxin to treat blepharospasm has proven popular for both physicians and patients. It is effective, safe, and easy to administer, although its effect is transient. The best method for injecting botulinum toxin, including both dosage and dose placement, has yet to be determined. Patients injected with 25 units per lower eyelid have shown a high incidence of diplopia⁷ which, in most cases, could

TABLE 1
SPASM-FREE INTERVAL AFTER BOTULINUM TOXIN
INJECTION

INJECTION METHOD	NO.	SPASM-FREE INTERVAL (WKS)		
		MEAN*	S.D.	RANGE
Toxin to upper eyelids, eyebrows, glabella, and lower eyelid areas	11	10.5	3.9	5–16
Toxin to upper eyelids, eyebrows, and glabella; saline to lower eyelid areas	15	11.8	4.6	4–20

^{*}The mean spasm-free intervals by injection methods are not significantly different (P > .3 by Student's *t*-test).

TABLE 2
INCIDENCE OF DIPLOPIA FOLLOWING BOTULINUM
TOXIN INJECTION

INJECTION METHOD	NO.	DIPLOPIA*	
		NO.	(%)
Toxin to upper eyelids, eyebrows, glabella, and lower eyelid areas	11	2	18.2
Toxin to upper eyelids, eyebrows, and glabella; saline to lower eyelids	15	Ó	0.0

be attributed to migration of the toxin in the lower eyelid to the inferior oblique muscle. Clearly, 25 units per lower eyelid is an inappropriately high dose. The two patients in this study who developed diplopia, each having received 7.5 units of botulinum toxin in each lower eyelid, had previously experienced diplopia after most lower eyelid injections, suggesting that they may have a facial defect that allows for easier passage of the toxin back to the inferior oblique muscle.

Careful notice should be given to the overall injection technique used in this study, since the spasm-free interval and diplopia incidence may be affected by varying methods and sites of toxin injection.

This study shows that botulinum toxin injection of the lower eyelid in patients with blepharospasm is not usually necessary to provide relief. Furthermore, omitting toxin from the

lower eyelid does not decrease the spasm-free interval. Since the inferior oblique muscle is closest to the medial two thirds of the lower eyelid, avoiding that site during toxin injection will likely result in little or no inferior oblique muscle paresis, while maintaining a high likelihood of relief of spasm.

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OPHTHALMIC MINIATURE

Tears, idle tears, I know not what they mean,
Tears from the depth of some divine despair
Rise in the heart, and gather to the eyes,
In looking on the happy autumn-fields,
And thinking of the days that are no more.

Alfred, Lord Tennyson, "Songs from The Princess," 1847

Allergic Lacrimal Obstruction

Ted H. Wojno, M.D.

Five patients with ocular allergy and intermittent epiphora had a temporary obstruction at the level of the lacrimal sac or canaliculus. The obstruction probably resulted from mucosal edema induced by rubbing the pruritic periocular tissues, a maneuver commonly performed by such patients. Treatment was aimed at inhibiting the allergic response with cromolyn sodium eyedrops, and patients were instructed to refrain from rubbing the periocular tissues.

EPIPHORA is caused by dacryocystitis, dacryostenosis, canalicular and punctal stenosis, hypersecretion, eyelid laxity, and ocular irritation. These conditions are usually easy to diagnose and treat. In some patients, however, the diagnosis is obscure or no symptoms are present on examination.

Epiphora is a common symptom of allergic conjunctivitis¹ and has been presumed to be caused by lacrimal hypersecretion stimulated by offending allergen.^{2,3} Although hypersecretion does occur, the five cases reported herein suggest that reversible lacrimal obstruction initiated by rubbing of the eyes is another mechanism by which epiphora might occur in patients with allergic conjunctivitis.

Subjects and Methods

I examined five patients with a long-standing history of intermittent epiphora. Although they were variably symptomatic throughout the year, four of five experienced worse symptoms in the spring and summer and had a documented history of atopic disease. All five patients noted that the epiphora was accompa-

nied by itching of the eyes, especially in the medial canthi. None of the patients had a history of dacryocystitis, nasal fracture, sinus disease, or surgery.

When initially examined, all five patients were asymptomatic. Routine lacrimal testing included the basic secretion tear test, the dye disappearance test, and the Jones primary and secondary dye tests. In the primary dye test, 2% fluorescein solution is placed in each culde-sac and cotton-tipped probes are placed beneath each inferior turbinate for ten minutes. If dye is recovered on the probe, the test is positive indicating patency of the lacrimal system. No dye indicates an obstruction. In the secondary dye test, the nasolacrimal duct is irrigated with water. If the fluid recovered from the nose is dye stained, the test is positive and indicates a functional block of the duct. Clear fluid only recovered from the nose indicates an obstruction in the lacrimal sac or canaliculus.

The patients were again examined when they felt symptoms suggestive of allergic conjunctivitis but they had been specifically instructed not to rub their eyes, even momentarily, on the day of the second examination. While in the office under observation, they were allowed to rub the pruritic ocular tissues of the right medial canthus only for 30 seconds. All five patients considered this rubbing to be a common, natural response to their irritation. All patients experienced the onset of epiphora within five minutes and lacrimal testing was then repeated. Two patients were also studied with lacrimal scintillography when asymptomatic and again when symptomatic.

Ten age-matched patients with no history of atopic disease or epiphora served as controls. They were given the same battery of lacrimal tests, and on the second visit, lacrimal testing was repeated after they had rubbed the right medial canthus for 30 seconds.

Results

When asymptomatic, the five patients showed no evidence of lacrimal obstruction

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From the Department of Ophthalmology, the Emory Clinic, Atlanta. This study was supported in part by an unrestricted grant from Research to Prevent Blindness, Inc.

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TABLE						
RESULTS OF LACRIMAL	TESTING					

PATIENT NO.	BASIC SECRETION TEAR TEST R.E./L.E. (MM)	DYE DISAPPEARANCE TEST R.E./L.E. (MIN)	PRIMARY DYE TEST R.E./L.E.	SECONDARY DYE TEST R.E.
Patient 1				
Asymptomatic	11/9	3/3	Positive/positive	-
Symptomatic	30/15	15/3	Negative/positive	Negative
Patient 2				
Asymptomatic	30/30	3/3	Positive/positive	
Symptomatic	35 at 1 min/25	15/3	Negative/positive	Negative
Patient 3				
Asymptomatic	35/30	4/4	Positive/positive	
Symptomatic	35 at 1 min/30	12/3	Negative/positive	Negative
Patient 4				
Asymptomatic	14/16	1/1	Positive/positive	
Symptomatic	35 at 2 min/25	15/1	Negative/positive	Negative
Patient 5		4		
Asymptomatic	22/26	2/2	Positive/positive	-
Symptomatic	35 at 3 min/15	15/3	Negative/positive	Negative

(Table). In the symptomatic, rubbed eye only there was both a large increase in tearing as measured by basic secretion tear test and a remarkable prolongation of the dye disappearance test, suggestive of unilateral lacrimal obstruction.

The primary dye test was positive (dye recovered in the nose) bilaterally in all five patients while asymptomatic. When symptomatic, however, the primary dye test was negative (no dye recovered in the nose) only in the eye that was rubbed for 30 seconds; results on the nonrubbed side remained positive. The secondary dye test, performed on each symptomatic, rubbed eye, was also negative (clear fluid only recovered from the nose) in all cases. The irrigation was performed without difficulty and the puncta were patent.

The results of lacrimal testing on the symptomatic, rubbed eye indicated that dye could not enter the nasolacrimal sac but that the duct was patent. An obstruction must have developed upon rubbing at the level of the lacrimal sac or canaliculi. The nonrubbed nasolacrimal system remained patent even though the eye was also pruritic. All five patients reported that the epiphora cleared within four hours if rubbing was not repeated.

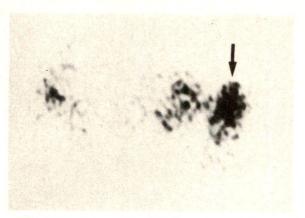
In the control group, lacrimal testing was positive both before and after rubbing the medial canthus. There was no evidence that rub-

bing induced any change in the nasolacrimal system of normal patients.

In the two patients studied by lacrimal scintillography, 4.5 the nasolacrimal systems were patent while they were asymptomatic, and the lacrimal sac was well filled with radio-active tracer by 25 seconds (Fig. 1). In the right, symptomatic eye after 30 seconds of rubbing the right medial canthus, the drainage system appeared completely blocked. The lacrimal sac could not be visualized even at 17 minutes, a grossly abnormal result. 4.5 The left, nonrubbed nasolacrimal system remained patent to tracer, even though this eye was symptomatic (Fig. 2). These results again suggested an obstruction at the level of either the lacrimal sac or canaliculi.

Three of these five patients were given cromolyn sodium, a mast cell stabilizer and blocker of the allergic response. All three patients reported complete relief of epiphora and symptoms of ocular irritation.

In the two years since this investigation, I have examined 21 patients referred for epiphora in whom the results of lacrimal tests were normal at the time of examination. Symptoms of ocular allergy were not volunteered but could be elicited from ten patients upon careful questioning (mainly about medial canthal itching). All ten patients were given cromolyn sodium eyedrops and instructed to avoid eye rubbing. Seven patients reported complete re-



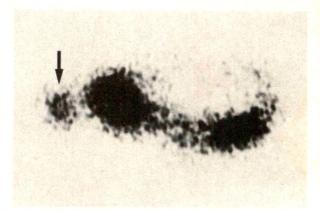


Fig. 1 (Wojno). Lacrimal scan showing bilateral patency of lacrimal system while patient is asymptomatic. Note rapid filling of lacrimal sacs (arrows) at 25 seconds after instillation of radioactive tracer (left, right eye; right, left eye).

lief of epiphora in one week and one patient felt greatly improved. The remaining two patients noted improvement.

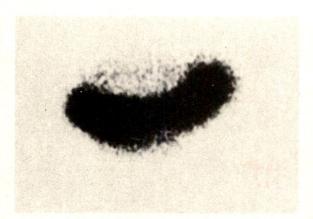
Discussion

Allergic or hay fever conjunctivitis is an immediate (type I) hypersensitivity response to airborne allergens such as pollens, mold, dust, and danders. It affects the conjunctival and nasal mucosa. In sensitized individuals, allergen binds with IgE antibody attached to mast cells of the eye and the nose. The activated mast cell then releases histamine and other mediators of inflammation into the surrounding tissue, causing itching of the medial canthal region, 6 vasodilation, and edema. 1

The patients complain of intense itching, especially over the medial canthi, photophobia, and tearing. They are also bothered by rhinorrhea, sneezing, and coughing. Examination shows conjunctival edema, hyperemia, and swelling of the eyelids. The nasal mucosa and turbinates may be swollen and pale. In mild cases, there may be no obvious abnormalities.

It has been assumed that epiphora in allergic conjunctivitis is caused by lacrimal hypersecretion from irritation by the allergen.^{2,3} Although Jones⁷ alluded to the occasional occurrence of punctal stenosis in allergic conditions, lacrimal obstruction has not been considered as a factor contributing to epiphora in these patients.

The five patients described here gave a history of intermittent epiphora that accompanied episodes of ocular irritation, most notably over the medial canthi. It is of particular note that



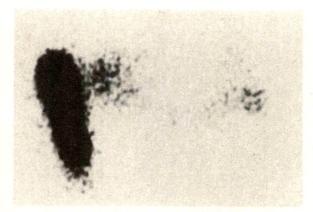


Fig. 2 (Wojno). Lacrimal scan of same patient as in Figure 1 showing complete obstruction of right lacrimal system when patient is symptomatic and has rubbed only the right medial canthus. Left, right eye; right, left eye. Tracer remains confined to palpebral aperture on the right even at 17 minutes but empties normally on the left.

these patients complained primarily of epiphora and not other symptoms of allergic conjunctivitis. Four of the five patients had a documented history compatible with atopic disease. While asymptomatic, results of lacrimal tests were normal, indicating patent nasolacrimal systems in all patients. When symptomatic, each patient was allowed to rub the right eye over the medial canthus for 30 seconds under observation. Each patient considered this maneuver to be the customary response to their ocular irritation. All patients experienced rapid onset of epiphora and lacrimal testing of the right eye at that time showed an obstruction at the level of either the canaliculi or lacrimal sac. The left (nonrubbed) nasolacrimal system of each patient remained patent although this eye was similarly symptomatic. All five patients reported that the epiphora cleared within four hours if eye rubbing was not repeated. These findings support the theory that mechanical obstruction of the canaliculus or lacrimal sac causes epiphora in some patients who have ocular allergies. Eye rubbing precipitates the episode of obstruction by causing mucosal edema within the lacrimal passages.

Greiner and associates8 studied the effect of eye rubbing on the histologic features of rat conjunctiva. They found that eye rubbing alone could induce mast cell degranulation, although not to the extent that occurs in ocular anaphylaxis. Eye rubbing also led to conjunctival vascular engorgement caused by vasoactive substances released by the mast cells. They concluded that eye rubbing could increase the severity of symptoms in ocular allergic conditions. It is uncertain if rubbing causes increased tear production. In the present study, there was no difference in the results of the basic secretion tear test in normal controls before and after rubbing, suggesting no increased tear production.

In patients with ocular allergy, rubbing the pruritic medial canthal tissues could promote further contact of allergen with the mucosa of the lacrimal sac and canaliculi. This could increase mast cell degranulation and release of vasoactive amines. The combination of eye rubbing and ocular anaphylaxis might thus potentiate the effect that each alone would have (Fig. 3).

Lacrimal outflow obstruction may occur at the level of the sac, canaliculus, or both in these patients. The lacrimal sac mucosa is surrounded by a rich venous plexus, similar to that found in erectile tissue. Vascular engorgement

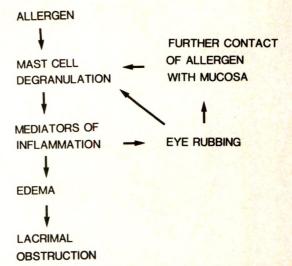


Fig. 3 (Wojno). Diagram of the potentiating effect of eye rubbing on the process of ocular allergy and subsequent lacrimal obstruction.

and tissue edema from ocular inflammation and eye rubbing could compress the sac and close its lumen. The canaliculi are only 0.5 mm in diameter,⁹ making it possible for edema in the surrounding tissues to obstruct temporarily their lumina. When the allergic reaction subsides, edema decreases and the sac or canaliculi are again patent.

It is not known why the medial canthal tissues are especially pruritic in allergic conjunctivitis. The antigen load may be greater in this region given the direction of tear flow. Certainly, the antigen concentration within the sac and canaliculi should be high and they themselves may become pruritic.

This study showed that only short periods of eye rubbing (30 seconds) were needed to obstruct the lacrimal system for several hours in patients with ocular allergy. Such a short period of rubbing may be unnoticed by a patient who has grown accustomed to many years of ocular irritation and rubbing. These patients may deny that they rub their eyes unless specifically questioned. As in the five patients described here, the patient may seek medical care for epiphora, not for ocular irritation.

The ten additional patients examined since this study who had symptoms suggestive of allergic lacrimal obstruction were treated with cromolyn sodium, a mast cell stabilizer and blocker of the allergic response. Seven patients experienced relief of epiphora. Cromolyn, by

blocking mast cell degranulation, relieves the urge to rub the eyes and thus breaks the cycle that leads to edema in the lacrimal system (Fig. 3).

Vasoconstrictor/antihistamine combination eyedrops may also be helpful in these patients, but they are effective against only one mediator of inflammation: histamine. Cromolyn prevents the release of all allergic inflammatory mediators and thus empirically seems more therapeutic. Some authors 10 believe that systemic antihistamine is preferable to topical antihistamine for general treatment of allergic conjunctivitis; however, treatment with cromolyn avoids the unwanted side effects of oral antihistamines (primarily drowsiness and gastrointestinal upset). Although there has been no double-masked study comparing cromolyn with either topical or oral antihistamine, some authors^{1,11} believe that cromolyn is the treatment of choice for allergic ocular disorders in general.

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OPHTHALMIC MINIATURE

. . . my method of simply closing my right eye when going in to record a sight and recover chronometer time, a method which also works when being called to the bridge by a panicked mate or when making head calls across boobytrapped staterooms on nasty nights. When both eyes are finally opened either in the light or dark the effect is passing weird, but is passing.

Norman Cubberly, "Readers Forum" in *The Navigator's Newsletter* Foundation for the Promotion of the Art of Navigation, Issue 20, Spring

Combined Viable Composite Grafting and Eyelid Sharing Techniques to Prevent Blepharoptosis After Extensive Tumor Excision

Allen M. Putterman, M.D., and Michael E. Migliori, M.D.

Five patients underwent tumor excision involving either the entire upper eyelid and temporal lower eyelid (three patients) or the entire lower eyelid and temporal upper eyelid (two patients), followed by reconstruction with an eyelid sharing procedure combined with viable composite grafting to the upper eyelid and a temporal semicircular flap. None of the five patients developed postoperative blepharoptosis, and all had excellent functional and cosmetic results. Follow-up ranged from 23 to 94 months.

EXTENSIVE EYELID TUMORS may require resection of parts of the upper and lower eyelids and lateral canthus. This large surgical defect can be difficult to reconstruct. There may be insufficient adjacent tissue to create a rotational or sliding flap to repair the defect without undue tension.

In most cases, the lower eyelid can be pulled taut without causing any functional or cosmetic difficulties. If the upper eyelid is too taut, blepharoptosis will result because of the bowstring effect caused by stretching the horizontally shortened upper eyelid between the medial and lateral canthal tendons.

Viable composite grafting has been described for reconstruction of temporal eyelid defects. We used this technique to add horizontal length to the upper eyelid remnant in patients who had undergone resection of their entire lower eyelid and temporal upper eyelid and also to add horizontal length to a Cutler-Beard type flap, which may otherwise be too narrow, in patients with resection of their entire upper

eyelid and temporal lower eyelid. This technique prevented postoperative blepharoptosis.

Material and Methods

We performed eyelid sharing procedures (either a tarsoconjunctival flap from the upper eyelid remnant or a Cutler-Beard type flap from the lower eyelid remnant) combined with viable composite grafting and a temporal semicircular flap on five patients after resection of eyelid tumors. Three patients had upper eyelid tumors extending onto the lateral canthus and temporal lower eyelid. Two of these patients had meibomian gland carcinomas, and the third had a basal cell carcinoma. Two additional patients had basal cell carcinomas involving the entire lower eyelid, lateral canthus, and temporal upper eyelid.

In all five patients, the tumors and full-thickness eyelids were excised under frozensection control, assuring that all margins were free of tumor. Three-millimeter margins of clinically normal tissue surrounding the tumor were excised along with the basal cell carcinomas. Five-millimeter margins were taken with the meibomian gland carcinomas.

The patients ranged in age from 59 to 75 years. Follow-up ranged from 23 to 94 months.

Reconstruction after resection of the entire upper eyelid and temporal lower eyelid—A Cutler-Beard type flap was created (Fig. 1, A).² A transmarginal rotation clamp or large chalazion clamp was applied to the lower eyelid.⁴ The medial upper eyelid remnant was pulled laterally until it was under slight tension, and the distance from its temporal edge to the lateral canthal tendon was measured. This distance determined the size of the lower eyelid flap. A horizontal incision was made 4 mm below the anterior eyelash border through skin and orbicularis muscle of the lower eyelid remnant, beginning at a point corresponding to the lateral edge of the upper eyelid remnant. The inci-

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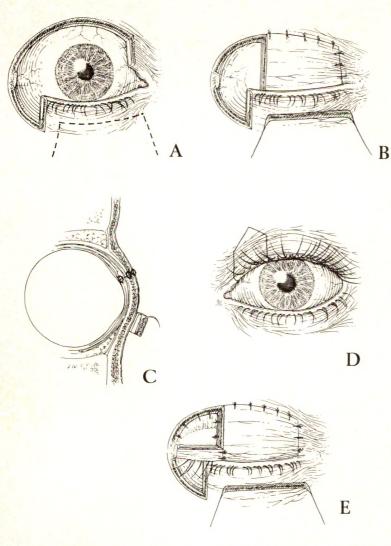


Fig. 1 (Putterman and Migliori). Reconstruction after resection of the entire upper eyelid and temporal lower eyelid. A, Outline Cutler-Beard flap. B, Cutler-Beard flap is sutured to defect in upper eyelid. C, Cross section of eyelid outlining suturing of Cutler-Beard flap to remaining upper eyelid. D, Composite graft taken from opposite nasal eyelid. E, Eyelid margin tarsoconjunctival composite graft component sutured into temporal upper eyelid defect.

sion was directed laterally and ended 4 to 5 mm from the lateral edge of the lower eyelid remnant to preserve the blood supply to the eyelid margin. The lower eyelid was everted with the clamp in place and a second horizontal incision was made 4 mm below the posterior eyelid margin through conjunctiva and tarsus in a similar horizontal dimension as the anterior incision. The tissue remaining between the two incisions was severed with Westcott scissors, completing the full-thickness blepharotomy.

Vertical incisions were made at each end of the horizontal incision, directed inferiorly, to create a full-thickness flap of the lower eyelid. This flap was passed beneath the margin bridge flap (Fig. 1, B). Conjunctiva and tarsus of the lower eyelid flap were sutured to conjunctiva and Müller's muscle of the upper eyelid remnant, and orbicularis muscle from the lower eyelid flap was sutured to the levator aponeurosis of the upper eyelid remnant with interrupted 6-0 Vicryl sutures. Skin was sutured to skin with interrupted 6-0 silk sutures (Fig. 1, C).

The distance from the lateral edge of the upper eyelid flap to the lateral orbital rim was measured by pulling the lateral aspect of the flap temporally to the point of slight tension. This determined the width of the composite graft, which was taken as a full-thickness pentagon from the opposite nasal upper eyelid (Fig. 1, D). A full-thickness vertical incision was made through the opposite upper eyelid margin with a No. 11 Bard-Parker blade. The incision was extended to the superior tarsal border. A Westcott scissors was used to sever full-thickness eyelid from the superior end of the incision obliquely to the proposed apex of the graft. A second vertical incision was made through the eyelid margin to create a graft equivalent to the upper eyelid defect. The pentagonal resection was completed with Westcott

scissors. The donor site was closed directly.³ If a large composite graft is taken, the donor site can be closed after a lateral canthotomy and cantholysis.³

A horizontal incision was made in the composite graft through skin and orbicularis muscle, 3 mm from the eyelash border. The skin and orbicularis muscle were removed with scissors. This left a composite graft consisting of tarsus, conjunctiva, and eyelid margin; a fragment of Müller's muscle and levator aponeurosis may still have been attached superiorly. The medial margin of the graft was sutured to the lateral margin of the Cutler-Beard flap with 6-0 silk sutures. The conjunctiva and tarsus of the graft were sutured to the conjunctiva and Müller's muscle of the temporal flap and upper eyelid remnant with interrupted 6-0 Vicryl sutures (Fig. 1, E). A 4-0 double-armed Vicryl suture was passed internally to externally through temporal tarsus of the graft. Both arms of the suture were then passed internally to externally through the periosteum of the lateral orbital rim at the previous lateral canthal tendon site (Fig. 2, A).

Both arms of a 4-0 Vicryl suture were passed internally to externally through tarsus at the lateral edge of the lower eyelid. Both arms of the suture were then passed internally to externally though periosteum of the lateral orbital rim at the previous lateral canthal tendon site (Fig. 2, A). Alternatively, the suture can be passed through a new lateral canthal tendon fashioned from a strip of periosteum attached to the lateral orbital rim.⁵

The tarsus of the composite graft was covered with a semicircular skin flap. A convex down semicircular flap was outlined on the skin beginning at the lateral canthal angle (Fig. 2, B). A skin incision was made, and the skin was undermined. The flap was then rotated to cover the tarsus of the graft and was sutured to surrounding skin with 6-0 silk sutures. Several 6-0 silk sutures also secured the skin flap to the anterior tarsus of the graft to ensure direct contact of skin to the graft (Fig. 2, C and D).

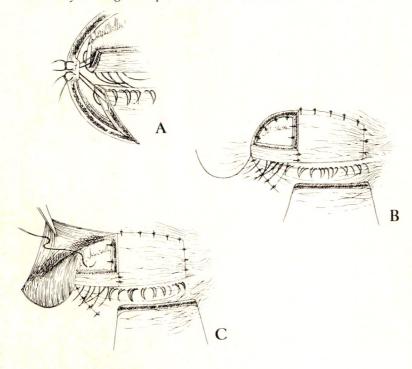
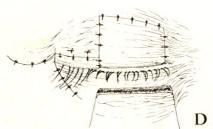


Fig. 2 (Putterman and Migliori). A, Suturing of temporal upper and lower eyelids to lateral canthal tendon. B, Outlining convex down semicircular temporal skin flap. C and D, Suturing of temporal semicircular skin flap over composite graft.



The inferior edge of the lower eyelid bridge flap was allowed to heal spontaneously.

Six weeks postoperatively, the flap was divided at the upper eyelid margin and the remaining flap was sutured to the inferior edge of the lower eyelid bridge flap.^{2,3}

Reconstruction after resection of the entire lower eyelid and temporal upper eyelid—The medial lower eyelid remnant was pulled laterally under moderate tension (Fig. 3, A). The distance from the temporal edge of the lower eyelid remnant to the lateral canthal tendon was measured. This determined the width of the tarsoconjunctival flap necessary to repair the lower eyelid defect. The upper eyelid remnant was everted over a Desmarres retractor (Fig. 3, B). A horizontal incision was made through conjunctiva and tarsus 4 mm above the

eyelid margin with a No. 15 Bard-Parker blade. The incision was begun at the temporal cut edge of the upper eyelid tarsus and was extended medially for a distance equal to the length of the lower eyelid defect. A vertical incision was made through tarsus at the medial end of the horizontal incision, extending to the superior tarsal border. Levator aponeurosis was dissected from the anterior tarsal surface with sharp iris scissors. Conjunctiva was undermined from Müller's muscle above the superior tarsal border to the upper fornix. The vertical incision was extended through conjunctiva superiorly.

Conjunctiva at the edge of the lower eyelid defect was separated from the retractors and Müller's muscle. The edge of the tarsoconjunctival flap was sutured to the edge of con-

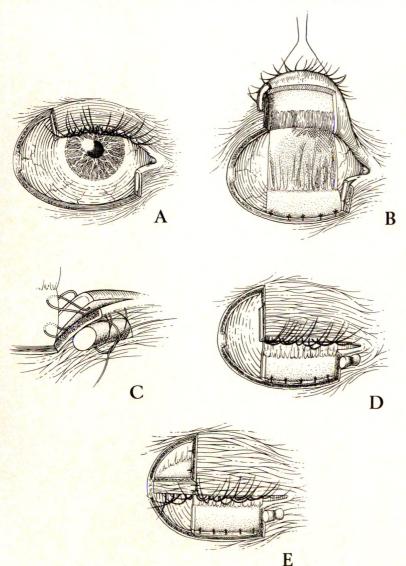


Fig. 3 (Putterman and Migliori). A, Reconstruction of defect after resection of entire lower eyelid and temporal upper eyelid. B, Tarsoconjunctival flap from upper eyelid sutured to lower eyelid defect. C and D, Suturing of nasal tarsoconjunctival flap to nasal lower eyelid remnant. E, Suturing composite graft to temporal upper eyelid.

junctiva of the lower eyelid with interrupted 6-0 Vicryl sutures. The end of the medial lower eyelid remnant was split for 2 mm at the gray line with a No. 11 Bard-Parker blade. Both arms of a 4-0 double-armed silk suture were passed from the conjunctival surface through tarsus of the medial lower eyelid remnant. Both arms of the suture were then passed through the medial edge of tarsus of the tarsoconjunctival flap, and then through orbicularis muscle and skin of the medial lower eyelid remnant. The suture ends were tied over a cotton pledget (Fig. 3, C). The upper eyelid flap was sandwiched between the anterior and posterior lamellae of the medial lower eyelid remnant.

The distance from the temporal edge of the upper eyelid remnant to the lateral orbital rim was measured after pulling the temporal edge laterally to the point of slight tension (Fig. 3, D). This determined the width of the composite graft, which was to be taken from the nasal opposite upper eyelid to reconstruct the defect (Fig. 1, D). The medial margin of the graft was sutured to the lateral margin of the upper eyelid remnant with 6-0 silk sutures. One suture was passed through tarsus and exited at the posterior eyelid margin, the second suture was passed through the gray line, and the third suture was passed through the most posterior

row of eyelashes. Each suture was tied in triplicate, and the anterior suture was tied over the posterior two sutures so that the suture ends pointed away from the eye. The tarsus of the graft was sutured to the tarsus of the upper eyelid with 6-0 Vicryl sutures. Conjunctiva, Müller's muscle, and levator aponeurosis were sutured to the superior tarsal border of the graft (Fig. 3, E). A 4-0 double-armed Vicryl suture was passed internally and externally through the lateral edge of tarsus of the graft. Both arms of the suture were then passed internally and externally through the periosteum of the lateral orbital rim at the previous lateral canthal tendon site (Fig. 4, A). A 4-0 double-armed Vicryl suture was passed through the lateral edge of tarsus of the tarsoconjunctival flap in an internal to external direction. Both arms of the suture were passed internally to externally though the periosteum of the lateral orbital rim at the previous lateral canthal tendon site (Fig. 4, A).

The tarsoconjunctival flap was covered with a retroauricular skin graft (Fig. 4, B through F). The composite graft was then covered with the convex down semicircular temporal skin flap (Fig. 4, C through E).

Six weeks postoperatively the flap was divid-

ed at the lower eyelid margin.3

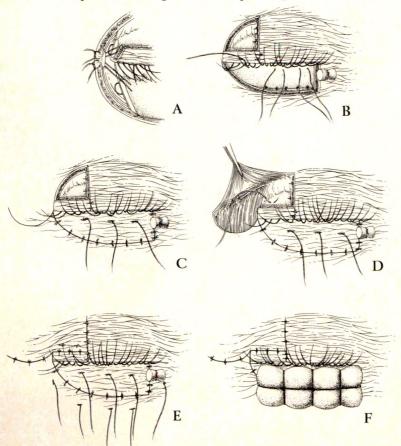


Fig. 4 (Putterman and Migliori). A, Suturing temporal composite graft and tarsoconjunctival flap to lateral canthal tendon. B and C, Suturing a posterior auricular skin graft to tarsoconjunctival flap. D and E, Temporal semicircular flap sutured over composite graft. F, Telfa pad sutured over skin graft.

Results

Three patients underwent resection of their entire upper eyelid and adjacent temporal lower eyelid to remove eyelid tumors (Fig. 5, left). In these three cases, a Cutler-Beard flap from the lower eyelid remnant was used to reconstruct the nasal upper eyelid, and a viable composite graft and semicircular skin flap were used to reconstruct the temporal upper eyelid (Fig. 5, right).

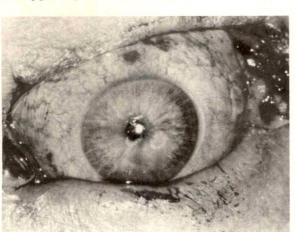
Two patients each had their entire lower eyelid and adjacent temporal upper eyelid resected (Fig. 6, left). In both cases, a tarsoconjunctival flap and retroauricular skin graft were used to reconstruct the lower eyelid, and a viable composite graft and semicircular skin flap were used to repair the upper eyelid defect (Fig. 6,

right).

None of the five patients developed postoperative blepharoptosis. Each of the five composite grafts survived without shrinkage, and in two patients the eyelashes on the graft survived. There were no complications involving the donor eyelids. These procedures produced excellent cosmetic and functional results. There have been no tumor recurrences. Follow-up ranged from 23 to 94 months.

Discussion

Blepharoptosis may result as a complication of upper eyelid reconstruction when upper



eyelid defects are closed with excessive tension. The upper eyelid cannot move up and down when it is too taut. Central defects can be closed after tension is relieved with a lateral canthotomy and cantholysis. However, when full-thickness temporal eyelid defects extend to the lateral canthus, there is insufficient tissue to slide nasally. In 1984, Putterman¹ described the combined viable composite graft and temporal semicircular flap procedure, which provides a simple method for the reconstruction of the temporal eyelid. Graft survival is increased by reducing the graft to an eyelid margintarsus-conjunctival component, and sliding a skin flap over the graft to nourish it.

Large upper eyelid defects can be repaired with a Cutler-Beard flap from the lower eyelid.^{2,3} When part of the lower eyelid is also resected, the lower eyelid flap is not wide enough to reconstruct the entire upper eyelid. Not only will the upper eyelid be too taut to elevate, but the horizontally narrow palpebral fissure may be cosmetically unacceptable. The addition of a composite graft to the upper eyelid increases its horizontal length, improving the cosmetic and functional result.

When the entire lower eyelid is resected, a tarsoconjunctival flap from the upper eyelid and a retroauricular skin graft can be combined to reconstruct the lower eyelid. ^{3,6} If the temporal upper eyelid is also resected, then a composite graft can be used to reconstruct this area, thus maintaining adequate laxity to permit the upper eyelid to elevate. The lower eyelid may be taut, but its mobility is not as important.

The eyelids consist of two lamellae. The ante-



Fig. 5 (Putterman and Migliori). Left, Surgical defect after excising meibomian gland carcinoma under frozen section control. The entire upper eyelid and the temporal 10 mm of the lower eyelid were excised. Right, Same patient three months postoperatively after reconstruction of upper eyelid and Cutler-Beard flap from lower eyelid and composite graft from opposite upper eyelid.

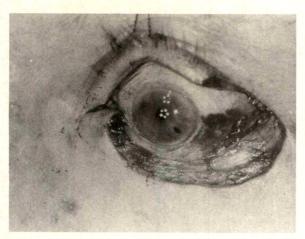




Fig. 6 (Putterman and Migliori). Left, Surgical defect after excising basal cell carcinoma under frozen section control. The excision extended from the lower punctum to the lateral orbital rim and included the temporal 15 mm of the upper eyelid. Right, same patient three months postoperatively after reconstruction of lower eyelid with tarsoconjunctival flap from upper eyelid and retroauricular skin graft and of upper eyelid with composite graft from opposite upper eyelid.

rior lamella is composed of skin and orbicularis muscle. The posterior lamella is made up of tarsus and conjunctiva. This posterior layer provides structural support for the eyelid as well as a mucous membrane-lined surface against the globe. These factors must be considered before attempting reconstruction of full-thickness eyelid defects.

Many techniques have been described for repair of large eyelid defects. Free tarsal grafts, nasal cartilage, and ear cartilage combined with myocutaneous flaps that provide blood supply to the free grafts can be used to repair full-thickness upper and lower eyelid defects.

Because the temporal upper and lower eyelids and lateral canthus were resected in each of our patients, there was insufficient adjacent tissue available for advancement of a temporal myocutaneous flap to reconstruct the entire defect in any case. Large free grafts would have been necessary. Large myocutaneous flaps would also have had to be mobilized from the cheek or forehead to cover the free grafts. Eyelid sharing techniques, either the Cutler-Beard flap or the tarsoconjunctival flap, provided the largest area of coverage with normal eyelid tissue.

Free cartilage grafts could have been used to add length to the upper eyelid, but these tend to stay thick, and mobility of the eyelid is often poor. The advantage of using a viable composite graft is that the graft consists of normal eyelid tissue, including the eyelid margin and eyelashes. These grafts usually give a superior cosmetic result.

We used this procedure on five patients. None developed postoperative blepharoptosis and all had good cosmetic results. Combining eyelid sharing techniques with viable composite grafting prevents blepharoptosis caused by excessive eyelid tension after reconstruction of large surgical defects.

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Accommodation and Convergence Insufficiency With Left Middle Cerebral Artery Occlusion

Kenji Ohtsuka, M.D., Hiroshi Maekawa, M.D., Makoto Takeda, M.D., Nobuharu Uede, M.D., and Susumu Chiba, M.D.

We studied accommodation and vergence eye movements in a patient with a left middle cerebral artery embolism. Accommodation was monitored by an infrared optometer with the accommodative target being controlled by a microcomputer. Computed tomography showed low-density areas in the left cortex, with intact brainstem. The patient had convergence palsy and accommodation abnormalities. The amplitude of the accommodative responses was reduced and the accommodation velocity was markedly lowered. Our results further substantiate the neurologic relationship between the cerebral cortex and accommodation and convergence.

Previous studies suggested that parietotemporal area was involved in the control of lens accommodation and vergence eye movements in the cat and the monkey.1,2 Jampel¹ demonstrated that convergence, lens accommodation, and pupil constriction were evoked by electric stimulus of the cerebral cortex surrounding the superotemporal sulcus of the monkey. Bando, Yamamoto, and Tsukahara² showed that neuronal activities of the lateral suprasylvian area of the cat were modulated before the onset times of lens accommodation and changed in temporal correlation with spontaneously occurring lens accommodation. It is known that the lateral suprasylvian area of the cat is homologous to the superotemporal sulcus of the monkey.3 However, whether the superotemporal sulcus area of the human brain is related to the control

of accommodation or vergence movements is uncertain. Recently, we found that these functions were disturbed in a patient with a left middle cerebral artery embolism. We performed neurologic, neuropsychologic, and neuro-ophthalmologic examinations in this patient. Accommodation was monitored by an infrared high-speed optometer, and the patient's dynamic and static responses were studied. Herein we describe the relationship between the lesion in the superotemporal sulcus area and accommodation and convergence insufficiency in this patient.

Case Report

A 31-year-old, right-handed man was admitted to our hospital after the sudden onset of aphasia and consciousness disturbance. Occlusion of the M1 portion of the left middle cerebral artery was observed by carotid arteriography (Fig. 1). An anastomosis between the left middle cerebral artery and the superficial temporal artery was immediately performed. After recovery from the consciousness disturbance, neurologic and neuropsychologic assessment demonstrated mild right hemiparesis, mild motor and sensory aphasia, and Gerstmann's syndrome (right-left disorientation, finger agnosia, acalculia, alexia, and agraphia). Computed tomography showed low-density areas lying near the sylvian fissure (inferofrontal, supramarginal, angular, superotemporal, and midtemporal gyri) and the putamen (Fig. 2). Abnormal shadows were not observed in the brainstem. The patient had blurred vision and diplopia with near vision. Convergence palsy was observed (Fig. 3). The convergence near point was about 1.5 m. However, external ophthalmoplegia was not present. Horizontal eye movements were examined by direct current electro-oculography. Saccadic eye movements were normal, but smooth pursuit eye movements were saccadic in both directions (Fig. 4).

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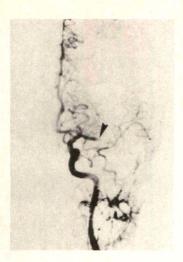




Fig. 1 (Ohtsuka and associates). Left carotid arteriography shows occlusion at the level of the M1 portion of the middle cerebral artery (arrowheads). Left, Anteroposterior projection and right, lateral projection of left carotid angiography.

Visual acuity in both eyes was 20/20, and the visual field was normal. Optic agnosia was not observed. Videopupillography showed no abnormalities of the pupillary light reflex.

Accommodation was monitored by an infrared high-speed optometer with a fixation target for accommodative stimulus and a television monitor for alignment of the eye position. The target was shaped like an asterisk, with four black lines radiating in eight directions located at the center of an illuminated field. The asterisk subtended an angle of 3 degrees, and the width of each line was 40 minutes of arc. The dioptric distance of the target was controlled by a microcomputer.

To study the dynamic response, we used the following paradigm. Since the patient was emmetropic, the accommodative stimulus was initially set at 0 diopter for five seconds. It was then abruptly changed to 4 diopters for ten

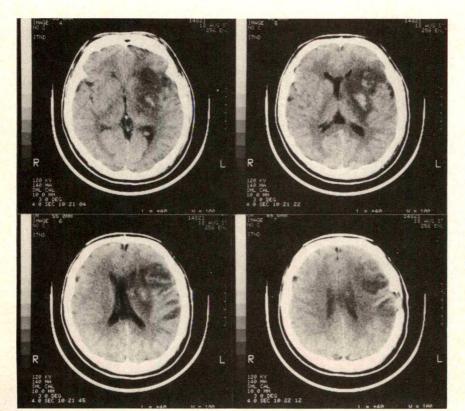


Fig. 2 (Ohtsuka and associates). Computed tomography shows low-density areas lying near the sylvian fissure (inferofrontal, supramarginal, angular, superotemporal, and midtemporal gyri) and the putamen.

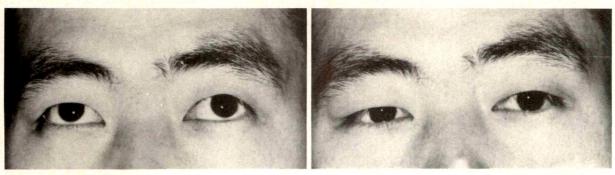


Fig. 3 (Ohtsuka and associates). Clinical appearance depicting the convergence palsy. Left, The eye positions during far vision and right, the eye positions during near vision.

seconds and then returned to 0 diopter. This paradigm was repeated five times. To study the static response, the target was moved from 0 to 10 diopters with a velocity of 0.2 diopter/second and then returned to 0 diopter. The accommodative response to this stimulus adequately described the static characteristics of accommodation. The patient was instructed to focus on the target continuously. The examination was performed two months after onset, and the patient had recovered from aphasia by this time.

We recorded accommodative responses and target diopters on each trial. Accommodation signals were digitized at 50 Hz. The entire system had a resolution of 0.01 diopter. Pupillary responses with accommodation were observed with a television monitor. The temporal characteristics of the dynamic accommodative response were quantified in terms of the latency and response times. The latency was taken as the length of time after the target change before any systematic changes in the amplitude of the optometer signal had occurred. The response time was taken as the length of time after the beginning of the change in signal

before the optometer signal leveled off at a steady value.

The dynamic responses are shown in Figure 5. The latency of far-to-near responses ranged from 400 to 440 msec. The far-to-near response time ranged from 2.6 to 4.5 seconds for 4diopter stimuli. Velocities of accommodation responses ranged from 0.6 to 1.0 diopter/ second. The near miosis accompanied by accommodation was observed by using the television monitor. The latency of near-to-far responses ranged from 280 to 310 msec. The near-to-far responses were biphasic (early and late components). The early component had a relatively fast velocity (about 0.6 diopter/ second). Accommodation reached 1.5 to 2.5 diopters by the early component. The response time of the early component ranged from 1.1 to 1.9 seconds for 0.8- to 1.4-diopter changes of accommodation. The late component had a low velocity (about 0.05 diopter/second), and accommodation did not reach the prestimulus level within the recording period. Thus, its response time could not be measured by using this system. The static responses are shown in Figure 5. The accommodation near point was

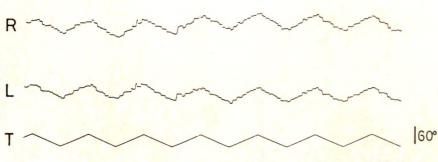


Fig. 4 (Ohtsuka and associates). Binocular electrooculogram showing saccadic pursuit. Upward deflections denote rightward movements. R, recording of the right eye; L, recording of the left eye; T, target movements.

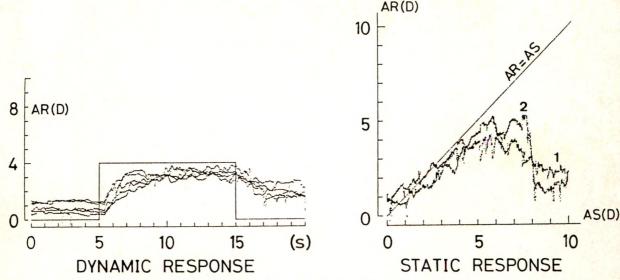


Fig. 5 (Ohtsuka and associates). Examples of dynamic (left) and static (right) responses of accommodation. Traces of dynamic responses consisted of five responses. The solid line indicates dioptric changes of the target. Traces of static responses consisted of a far-to-near response (trace 1) and a near-to-far response (trace 2). AR, accommodation response; AS, accommodation stimulus.

5.2 diopters. The slope of the accommodative response/accommodative stimulus was 0.75. There were no differences in dynamic and static accommodation responses between the right and left eyes.

Discussion

We found accommodation and convergence insufficiency in our patient. The latency of accommodative responses was slightly longer than that shown previously in normal subjects.⁵ In normal subjects, the response time (mean \pm S.D.) was 0.80 \pm 0.15 second for far-to-near responses and 1.24 ± 0.57 second for near-to-far responses.5 In our patient the near-to-far response time, which was estimated to be 20 to 30 seconds, was significantly prolonged. Additionally, the biphasic response observed in our patient has not been observed in normal subjects. The study of the static response showed depression of the accommodation amplitude. The normal range of accommodation amplitude in 31-year-old individuals is 7 to 11 diopters. 6 The slope of the accommodation response/accommodation stimulus in our patient was in the lower limit of the normal range (0.85 ± 0.06) .

The present study indicates that the left corti-

cal area, perfused by the middle cerebral artery, is related to the control of lens accommodation and convergence eye movements. Parasympathetic neurons in the Edinger-Westphal nucleus were intact in this patient because there was a normal pupillary light reflex. Thus, the accommodation abnormalities were not caused by abnormalities of the midbrain or the oculomotor nerve. It is well known that acquired convergence palsy is often caused by the dorsal midbrain syndrome. This syndrome is also associated with abnormalities in vertical gaze. However, eye movement abnormalities other than convergence palsy were not observed in our patient. Additionally, computed tomography did not disclose any abnormalities in the midbrain.

The accommodation system in humans operates as a feedback control system, with retinal blur as the input and the dioptric level of the lens as the output. The vergence system also operates as a feedback control system, with binocular disparity as the input and the alignment of two eyes as the output. The responses of the two systems are coordinated in time by cross-link interactions that allow stimuli to either system to activate both systems. Thus, the controller of each of the two systems is probably located in the same or neighboring area of the cortex. According to the studies of Jampel¹ and Bando, Yamamoto, and Tsukahara,² corti-

cal areas in and around the superotemporal sulcus are related to the control of lens accommodation and convergence eye movements. It is well known that neurons in the posterior bank of the superotemporal sulcus respond to a change in binocular disparity. 7,8 Binocular disparity is one of the indications for the control of vergence or lens accommodation. Thus, a lesion of the superotemporal sulcus was probably related to accommodation and convergence insufficiency in our patient. Computed tomography demonstrated low-density areas in and around the superotemporal sulcus. Sensory aphasia and Gerstmann's syndrome suggested neurologic disorders around the superotemporal sulcus area. Additionally, Dürsteler, Wurtz, and Newsome9 indicated that pursuit deficits were caused by a small lesion of the posterior bank of the superotemporal sulcus. The same deficits were also observed in our patient.

Accommodation-related neurons in the cortex project to the superior colliculus and the pretectum.2 The latter structure is monosynaptically connected to the parasympathetic oculomotor nucleus. 10 Therefore, the controller of lens accommodation is probably located in the superotemporal sulcus area. Insufficiency of the accommodation controller would be related to the prolongation of the accommodation response time and the decrease of accommodation amplitude, which occurred in our patient. However, our knowledge of the vergence controller is still incomplete. Vergence-related neurons have not been found in the cortex, but the superotemporal sulcus area appears to be related to depth discrimination in the visual space^{7,8} and the control of accommodative vergence. 1.2 There is no convincing evidence that the lesion of the superotemporal sulcus area was the only cause of the convergence

palsy in this patient. Further studies are needed to clarify the vergence control system in the cortex.

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OPHTHALMIC MINIATURE

Gray haunted eyes, absent-mindedly glaring
From wide, uneven orbits; one brow drooping
Somewhat over the eye
Because of a missile fragment still inhering,
Skin deep, as a foolish record of old-world fighting.

Robert Graves, "The Face in the Mirror," 1958

Immunohistochemical Evidence of Heterogeneity in Macular Corneal Dystrophy

C. Julia Yang, M.S., Nirmala SundarRaj, Ph.D., Eugene J.-M. A. Thonar, Ph.D., and Gordon K. Klintworth, M.D.

We used the avidin-biotin complex immunoperoxidase technique to test the reactivity of the abnormal corneal accumulations with five different monoclonal antibodies that recognize specific determinants on keratan sulfate. Eighty-eight corneas from 67 patients with macular corneal dystrophy were immunolabeled with the antibodies. In 31 corneas the abnormal accumulations did not react with any of the antikeratan sulfate antibodies, but 18 corneas reacted with all of the antibodies. The remaining corneas reacted with various combinations of the antibodies. The data suggest that the accumulations in macular corneal dystrophy are not always identical and that keratan sulfate is present in some cases but not in others. Thus, based on differences in the storage material, macular corneal dystrophy appears to manifest heterogeneity with at least two distinct varieties: keratan sulfate negative (type 1) and keratan sulfate positive (type 2).

MACULAR CORNEAL DYSTROPHY is characterized clinically by the presence of bilateral cloudy corneal stromas with superimposed discrete white opacities that merge as they progressively enlarge with time. Characteristic morphologic abnormalities involve the corneal stroma, Descemet's membrane, and the corneal

endothelium.¹⁻⁶ A striking feature of the tissue abnormalities is the intracytoplasmic accumulations within the fibroblasts and endothelial cells of the cornea, with histochemical features of glycosaminoglycans, ^{1,2,7-9} and extracellular accumulations within the corneal stroma and Descemet's membrane.

The storage material in macular corneal dystrophy has been suspected of being related to keratan sulfate because of its histochemical reactivity. Analyses of products of organ cultures of corneas, as well as of serum and corneal extracts in patients with macular corneal dystrophy, have supported the theory that the basic defect involves keratan sulfate. 10-16 Several investigators¹⁷⁻²² have produced monoclonal antibodies that recognize epitopes of keratan sulfate, which has opened up new possibilities for the identification of the accumulations. In this study we determined the reactivity of the abnormal accumulations in tissue sections of corneas with macular corneal dystrophy to five antikeratan sulfate monoclonal antibodies to establish whether the storage material exhibited attributes of keratan sulfate.

Material and Methods

Case material—Paraffin-embedded formalin-fixed corneal tissue from 88 corneas of 67 patients with macular corneal dystrophy were obtained from numerous sources. In all cases the diagnosis was based on the clinical features of the diseases and the histopathologic characteristics were confirmed by histochemical stains (Figure). The corneas of both eyes were studied in 15 patients. Corneal tissue from two siblings was studied in seven families and from three siblings in one family.

Immunoperoxidase staining—Tissue sections 5 µm thick from 88 corneas were mounted on Histostik-coated glass slides and processed using the avidin-biotin complex immunoperoxidase technique of Hsu, Raine, and Fanger.²³

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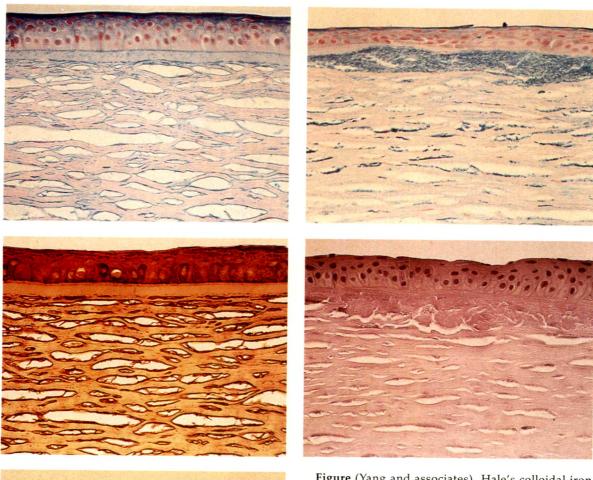




Figure (Yang and associates). Hale's colloidal iron preparations of normal cornea (top left) and of cornea with macular dystrophy containing abnormal blue staining accumulations (top right). Avidinbiotin complex immunoperoxidase preparations of normal cornea (middle left) and of cornea with macular dystrophy shows no reactivity (macular corneal dystrophy type 1) (middle right) or positive reactivity (macular corneal dystrophy type 2) (bottom left) to monoclonal antibodies to keratan sulfate. Type 1 specimens did not react with any of the antikeratan sulfate antibodies (MZ-15, J-10, J-19, J-20, or 1/20/5-D-4), whereas type 2 specimens reacted with all of these antibodies (×208).

Five murine antikeratan sulfate IgG monoclonal antibodies (MZ-15, 1/20/5-D-4, and three antibodies prepared by one of us [N.S.]: J-10, J-19, and J-20). These antibodies, which all recognize carbohydrate determinants in type 1 (corneal) and type 2 (cartilaginous) keratan sulfate, were prepared against porcine chondrocytes (MZ-15), 19,21 human articular cartilage proteoglycan (1/20/5-D-4),17,21 and rabbit corneal proteokeratan sulfate (J-10, J-19, and J-20). 18,22 The optimum working dilution and relative reactivity of each antibody were determined by visualizing their reactions with the avidinbiotin complex immunoperoxidase technique against normal corneal sections and against serial dilutions of corneal extracts that had been dotted onto nitrocellulose paper with appropriate controls.

The immunoperoxidase-prepared corneal sections were evaluated by light microscopy for positive or negative staining. Background staining was determined by control slides for each cornea in which the primary antibody was replaced with either nonimmune mouse serum

or bovine serum albumin.

Serum keratan sulfate levels—Without previous knowledge of the immunohistochemical evaluations, the serum keratan sulfate levels were determined in the laboratory of one of us (E.J.-M.A.T.) in 11 patients by an enzymelinked immunosorbent inhibition assay using antikeratan sulfate antibodies as previously described. 16,24

Correlations—The immunohistochemical data were correlated with available clinical, histopathologic, and genealogic information, as well as with serum keratan sulfate levels.

Results

Immunohistochemical findings—The corneas with macular corneal dystrophy could be divided into four immunohistochemical groups according to their pattern of reactivity with the five antikeratan sulfate antibodies (Table). Thirty-one corneas (28 patients) reacted negatively to all five antibodies (Group 1) (Figure, middle right), whereas 18 corneas (14 patients) reacted positively to all five antibodies (Group 2) (Figure, bottom left). Sections from 30 corneas reacted positively to MZ-15, J-10, and J-20, but negatively to J-19 and 1/20/5-D-4 (Group 3). The nine remaining corneas reacted randomly to the antibodies (Group 4).

To check whether the negative reactivity to J-19 and 1/20/5-D-4 in Group 3 corneas was caused by the weaker titers of these two antibodies (data not shown), five corneas of this variety were restained with undiluted J-19 and 1/20/5-D-4. This resulted in positive, but less intense, staining than the corneas in Group 2. In Group 2 corneas, the macular corneal dystrophy accumulations stained intensely with diluted antibodies.

Relation of immunochemical reactions to serum keratan sulfate levels—Serum was available for analysis from 11 patients (five from Group 1 and six from Group 2). In all instances of corneas manifesting no reactivity to any of the antibodies (Group 1) keratan sulfate was not detectable in the serum. However, the serum in the six patients whose corneas reacted positively to the five antibodies (Group 2) all contained detectable amounts of keratan sulfate (33, 356, 207, 435, 206, and 74 µg/ml). Serum was not available for analysis in any of the patients in Groups 3 or 4.

Differences between groups—The apparent age of onset, age at time of corneal graft, interval between onset and graft, and sex of the patients in the different groups are compared in the Table. Eleven of the 14 patients whose corneas reacted with all antikeratan sulfate antibodies were women. The mean age at apparent onset and at the time of grafting, as well as the duration of time from the apparent age of onset to grafting, tended to be greater in patients in Group 2 than in patients in the other

groups (Table).

Comparison between corneas in patients with bilateral keratoplasty—The corneal tissue from both eyes of 12 of the 15 pairs of corneas with macular corneal dystrophy from individuals who had undergone bilateral keratoplasty demonstrated identical immunohistochemical reactivity. In the other three pairs of corneas the reactivity in one cornea was that of Group 1 or Group 3, whereas the other cornea reacted randomly to the antibodies (Group 4).

Comparison between corneas from affected siblings—The immunohistochemical reactivity of corneas with macular corneal dystrophy from affected siblings were identical in four families. Two siblings in each of two families from Group 1 did not react with any of the antikeratan sulfate antibodies, whereas two siblings in each of two families in Group 3 reacted with monoclonal antibodies MZ-15, J-10, and J-20, but not with J-19 and 1/20/5-D-4. In four other families at least one sibling had

TABLE
AGE-RELATED COMPARISONS BETWEEN THE SUBTYPES OF MACULAR CORNEAL DYSTROPHY

GROUP	NO. OF	NO. OF		SE	EX	APPARENT AGE OF AGE OF ONSET (YRS) GRAFT (YRS)			INTERVAL BETWEEN ONSET AND GRAFT (YRS)		
NO.	CORNEAS	PATIENTS	М	F	UNKNOWN	MEAN	(RANGE)	MEAN	(RANGE)	MEAN	(RANGE)
1	31	28	15	12	1	20.3	(2-30)	38.6	(20-54)	17.9	(5–26)
2	18	14	3	11	_	23.3	(6-22)	51.2	(31–58)	28.8	(9–39)
3	30	24	11	11	2	26.6	(10-29)	35.9	(29-60)	20.3	(19–32)
4	9	9	7	2	_	13.5	(10-50)	32.8	(30–66)	23.5	(16–33)

the characteristics of Group 1, whereas the cornea of the other sibling manifested attributes of Group 2, Group 3, or Group 4 (two families).

Discussion

This study of 88 corneas from 67 histopathologically confirmed cases of macular corneal dystrophy detected differences in the reactivities of macular corneal dystrophy corneal tissue sections to antikeratan sulfate antibodies. The variations could be classified into four groups: 31 corneas that reacted negatively to all five antibodies (Group 1); 18 corneas that reacted positively to all five antibodies (Group 2); 30 corneas that reacted positively to MZ-15, J-10, and J-20 but negatively to J-19 and 1/20/5-D-4 (Group 3); and nine corneas that reacted randomly to the antibodies (Group 4).

The observation that certain corneas react with antikeratan sulfate antibodies strongly suggests that keratan sulfate is present in the accumulations of at least some cases of macular corneal dystrophy. Keratan sulfate was recently found to be absent from the serum of 16 patients with macular corneal dystrophy. 16 In the present study, serum analyses were performed on 11 cases using the same procedure, and the immunostaining correlated with the serum levels of keratan sulfate. Keratan sulfate was not detectable in the serum of patients whose corneas were nonreactive with all monoclonal antibodies to keratan sulfate, but was present in normal amounts in the serum of cases with immunoreactive corneal accumulations. Together these immunohistochemical and serum findings strongly suggest that at

least two varieties of macular corneal dystrophy exist, namely keratan sulfate-negative macular corneal dystrophy (type 1) and keratan sulfate-positive macular corneal dystrophy (type 2).

It is noteworthy that the best-described antikeratan sulfate antibodies, including 1/20/5-D-4, do not recognize unsulfated keratan sulfate. 16,17 The finding of corneas with macular dystrophy with abnormal accumulations that do not react with any of the antikeratan sulfate antibodies indicates that their accumulations do not share antigenic determinants with keratan sulfate. These results conform to the current concept that macular corneal dystrophy is a systemic disorder of keratan sulfate biosynthesis and that the corneal accumulations are either an abnormal keratan sulfate-related molecule or another carbohydrate-rich substance, 11,13,14 and that a specific sulfotransferase needed in the sulfation of the lactosaminoglycan backbone of keratan sulfate chain may be defective in macular corneal dystrophy. 14

Keratan sulfate was also virtually absent in extracts of one cornea with macular corneal dystrophy studied by Hassell and associates²⁵ and in five corneas with macular corneal dystrophy reported by Klintworth and associates.¹⁵ In immunohistochemical evaluations, Sundar-Raj and colleagues^{22,26} found that several monoclonal antibodies against keratan sulfate did not react immunochemically with three corneas with macular corneal dystrophy.

Identical or similar syndromes sometimes result from different genetic mutations, ²⁷⁻²⁹ such as allelic variability at a single locus, or variability at multiple loci, or a combination of both. ^{28,30} The findings in the present study support an earlier contention based on differences between corneas with macular corneal dystrophy

in culture and clinicopathologic data on over 220 cases of macular corneal dystrophy that the disorder is not homogeneous. 13 While an understanding of the nature of this heterogeneity awaits detailed analyses of the macular corneal dystrophy genome, mutations at different genetic loci may conceivably cause distinct enzymatic defects that affect separate points in the metabolism of keratan sulfate. If the abnormality affects the synthetic pathway, then intermediate metabolites preceding the blockade would accumulate. Undersulfated, or unsulfated, precursors of keratan sulfate moieties that do not react with the antikeratan sulfate antibodies may accumulate under such conditions as in type 1 macular corneal dystrophy. Type 2 macular corneal dystrophy could represent individuals having a defect in the catabolism of keratan sulfate.

As expected, the intrafamilial immunohistochemical reactivities of corneas with macular corneal dystrophy were identical in four families. However, in four other families differences were found in the corneal tissues of affected siblings. When this occurred type 1 was associated with type 2 or with a family member having random reactivity with the antikeratan sulfate antibodies. The significance of these observations remains unclear. If the finding is of biologic significance, it may indicate that more than one genetic locus is involved in the expression of macular corneal dystrophy. Since macular corneal dystrophy is known to have an autosomal recessive mode of inheritance, both parents would be expected to be carriers of the same mutant locus for macular corneal dystrophy. If parents are carriers of two mutant loci, different phenotypes of macular corneal dystrophy may occur in a single family, but the odds of this happening are extremely low. It seems more probable that the negative reaction to keratan sulfate antibodies in the one sibling reflects a blockage of keratan sulfate antigenic determinants caused by tissue processing.

The finding of identical immunochemical reactivity in the left and right corneas in 12 of the 15 pairs of corneas in which tissue from each eye was available for study is consistent with the belief that the same disorder affects both eyes. Moreover, since one would expect an individual to have the same genetically determined disease in both eyes it is noteworthy that all type 1 or type 2 cases manifested the same type in both corneas. The variability in the immunohistochemical reaction within the corneas of the remaining three pairs of eyes is

compounded in that one eye always demonstrated random reactivities to the antibodies. These random differences probably reflect vagaries of tissue processing rather than differences in the nature of the storage material in the two eyes.

The 30 corneas that reacted positively to MZ-15, J-10, and J-20, but negatively to J-19 and 1/20/5-D-4 (Group 3) may belong to the keratan sulfate-positive variety of macular corneal dystrophy (type 2) and the failure of antibodies J-19 and 1/20/5-D-4 to react with them may reflect the lower titer in the nonreacting antibody preparations. As demonstrated by dot blotting, our preparations of the antibodies J-19 and 1/20/5-D-4 had lower titers than the other antikeratan sulfate antibodies. However, since the epitopes that are recognized by the different monoclonal antibodies used in this study have not been fully characterized, it is also conceivable that they recognize different parts of the keratan sulfate molecule as alluded to by other investigators. 18,21 More information is needed to determine if the variability in staining in the Group 3 cases is a result of titer differences between the antibodies or minor structural difference in the accumulations between the different subgroups of macular corneal dystrophy.

The possibility that the immunochemical reactivities reflect an artifact of tissue processing is difficult to reconcile given the results found in specimens from Groups 1 and 2, especially in view of the associated serum keratan sulfate levels. However, the nine corneas that reacted randomly to the antibodies in an unpredictable manner probably represent vagaries in tissue processing rather than something of biologic significance. Variations in fixatives and fixation time are known to affect the preservation of certain antigens^{31,32} and embedding in paraffin also affects the availability of the antigenic determinants to antibodies. 31-33 Because several different interpretations of the findings in those specimens falling into Groups 3 and 4 are possible, these two groups cannot be considered as distinct types of macular corneal dystrophy on accessible evidence.

Future investigations on macular corneal dystrophy need to take into account the heterogeneity of macular corneal dystrophy as reflected by the immunohistochemical findings. In view of potential difficulties with paraffinembedded tissue, immunochemical studies should ideally be carried out on unfixed frozen tissue.

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OPHTHALMIC MINIATURE

A number of memories come back to me as I think of the house. I liked to peep into the larder, where there were many things beside the partridges and other game....In an old house there would be a deep-set window in the thickness of the wall, covered on the outside with perforated zinc and on the inside with white muslin stretched on a wooden frame. It was on the north side of the house so that no sun could shine in. Through the gauze one could see a dim, hazy view of the garden, and if anyone passed by the crunching of their feet was accompanied by a half-shadow, half-reflection, which moved across the ceiling in the opposite direction to that of the walker.

Harold Gaster, A Morning Without Clouds New York, St. Martin's Press, 1982, p. 13

Visual Results After Keratoplasty in Patients With Posterior Chamber Intraocular Lenses

Michael S. Insler, M.D., Craig J. Helm, B.S., and Herbert E. Kaufman, M.D.

We performed penetrating keratoplasty in 20 consecutive patients who had posterior chamber intraocular lenses and who developed pseudophakic bullous keratopathy. All patients received 8.0-mm grafts placed in 7.5-mm recipient beds. None of the intraocular lenses were removed. Final visual acuity was 20/40 or better in eight (40%) and 20/80 or better in 15 (75%) of the patients. Senile macular degeneration (one case), corneal graft rejection (two cases), and wound infection (one case) contributed to poor visual results in the remaining patients.

THE INCIDENCE of pseudophakic bullous keratopathy has risen in association with the increased use of intraocular lenses for the correction of aphakia. Today, pseudophakic bullous keratopathy is the leading indication for penetrating keratoplasty.1 Although many studies of corneal transplantation for pseudophakic bullous keratopathy have been published,²⁻¹¹ most have been concerned with patients who had anterior chamber or iris-fixated intraocular

Currently, cataract surgeons use predominantly posterior chamber intraocular lenses after planned extracapsular cataract extraction because the implantation of this lens appears to produce fewer complications and better visual results than the older types of intraocular lenses. 12 The incidence of pseudophakic bullous keratopathy after posterior chamber intraocular lens implantation has been reported to be lower than the rate associated with anterior chamber or iris-fixated intraocular lenses. 6,12 Factors that contribute to a reduction in the

incidence of corneal edema after posterior chamber lens implantation may also play a role in improved results after corneal transplantation in those eyes that develop pseudophakic bullous keratopathy.

In this study, we examined the results of corneal transplantation in a series of 20 patients with pseudophakic bullous keratopathy associated with posterior chamber intraocular lenses.

Patients and Methods

Twenty cases of pseudophakic bullous keratopathy associated with posterior chamber implants were referred to one of two of us (M.S.I. or H.E.K.) for penetrating keratoplasty between December 1984 and March 1987. All patients had undergone extracapsular cataract extraction with insertion of posterior chamber intraocular lenses. The implanting surgeon was not aware of any intraoperative complications or increased difficulty in lens insertion. In 17 (85%) of the 20 patients, the onset of corneal edema was noted by the first postoperative day. Two additional patients developed corneal edema gradually over a period of several weeks after surgery.

We used a double running suture technique for penetrating keratoplasty in 11 eyes, and eight interrupted 10-0 nylon sutures and a 16-bite continuous running 10-0 nylon suture in nine eyes. All grafts were 8.0 mm in diameter. The 7.5-mm recipient openings were cut with the Hessburg-Barron vacuum trephine. During the course of corneal transplantation, the intraocular lenses were inspected for fixation and centration. No intraocular lenses were removed. Postoperatively, follow-up examinations included assessment of best corrected visual acuity, pachymetry, corneoscopy, and tonometry. In the group having the double running sutures, the running 10-0 nylon suture was removed by three months after surgery. In the other group, the interrupted sutures were removed by three months after surgery. Spec-

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tacles or hard contact lenses were fit to achieve best corrected visual acuity.

Results

The average age of the patients was 68.9 years (range, 49 to 85 years). The average time interval elapsed between cataract surgery and penetrating keratoplasty was 10.3 months (range, two to 30 months). Follow-up after penetrating keratoplasty averaged 14 months (range, five to 26 months).

Eight (40%) of 20 patients achieved a visual acuity 20/40 or better (Table 1). Fifteen patients (75%) achieved a visual acuity of 20/80 or better. One patient had a visual acuity of counting

TABLE 1
RESULTS OF PENETRATING KERATOPLASTY FOR PSEUDOPHAKIC BULLOUS KERATOPATHY WITH POSTERIOR CHAMBER INTRAOCULAR LENSES

PATIENT NO., AGE (YRS), SEX	VISUAL ACUITY*	LENGTH OF FOLLOW-UP (MOS)	COMMENT
1, 68, F	20/70	15	Epithelial defect
2, 55, M	20/30	18	Cystoid macular edema,
			posterior capsulotomy
3, 49, F	20/20	24	_
4, 63, F	20/40	15	
5, 63, M	20/20	26	Posterior capsulotomy, rejection
6, 85, M	20/40	12	-
7, 66, F	20/40	22	Epithelial defect
8, 50, M	20/60	5	_
9, 75, F	CF	16	Senile macular
			degeneration
10, 75, M	20/300	10	Rejection
11, 70, M	20/50	12	_
12, 62, F	20/200	12	
13, 61, F	20/200	13	Rejection
14, 74, F	20/40	13	_
15, 76, M	20/50	12	_
16, 77, F	20/200	5	Regraft, wound infection
17, 74, F	20/80	13	_
18, 79, F	20/40	14	_
19, 84, F	20/80	14	Senile macular degeneration
20, 72, F	20/50	10	Wound infection, posterior capsulotomy

^{*}Best corrected Snellen acuity; CF, counting fingers.

fingers 16 months after surgery as a result of senile macular degeneration. One patient developed a transient case of cystoid macular edema; the occurrence and resolution were documented by fluorescein angiography. Increased intraocular pressure in previously normotensive eyes was observed in three patients but was well controlled with timolol maleate. One of these three patients was found to have developed an iridocorneal adhesion of 180 degrees temporally. Three patients developed posterior capsular opacification requiring Nd:YAG laser capsulotomy. Two patients developed persistent epithelial defects that reepithelialized after tarsorrhaphy. One patient developed a corneal plaque (wound infection) five months after surgery, which progressed to graft failure. Regrafting was subsequently done in this patient. Three additional patients experienced rejection reactions, a single episode in one patient and multiple episodes in the other two. Reactions in two of these patients were reversed with topical corticosteroids. Eighteen (90%) of the 20 grafts remained clear.

Discussion

Although assessments of complication rates with posterior chamber intraocular lenses are based on relatively short follow-up, these lenses have been associated with fewer complications, such as corneal edema, compared with anterior chamber and iris-fixated lenses. 6,12,13 We were interested in determining the results of penetrating keratoplasty in the subgroup of patients with posterior chamber intraocular lenses who develop pseudophakic bullous keratopathy.

We compared the results of earlier series involving penetrating keratoplasty in association with anterior chamber and iris-fixated intraocular lenses (Table 2) with our results and those of others describing patients who underwent penetrating keratoplasty in association with posterior chamber intraocular lenses (Table 3). The older series (Table 2) presented combinations of cases involving intraocular lens retention, removal, and exchange, as well as cases in which cataract removal was either intracapsular or extracapsular. There are only a few cases in the more recent series involving posterior chamber lenses (Table 3). The variations in the older series and the scarcity of

TABLE 2
RESULTS OF PENETRATING KERATOPLASTY FOR PSEUDOPHAKIC BULLOUS KERATOPATHY
IN TEN PUBLISHED SERIES

INVESTIGATORS, YEAR	NO. OF EYES	NO. OF POSTERIOR CHAMBER INTRAOCULAR LENSES	NO. OF CLEAR GRAFTS (%)	NO. WITH VISUAL ACUITY OF 20/40 OR BETTER (%)	AVERAGE FOLLOW-UP (MOS)
Meyer and Sugar,					
1980 ²	25	0	22 (88)	13 (52)	20.0
Charlton, Binder, and			,	()	
Perl, 1981 ³	19	1	18 (95)	3 (16)	13.1
Waltman, 19814	36	0	33 (92)	13 (36)	>12.0
Arentsen and Laibson,			,	(/	
1981 ⁵	36	1	34 (94)	12 (33)	18.0
Taylor and coworkers, 19836	42	0	37 (88)	10 (24)	18.0
Waring and coworkers, 19837	35	0	32 (91)	5 (14)	14.8
Kozarsky and coworkers,					
1984 ⁸	26	4	21 (81)	8 (31)	24.5
Schanzlin and coworkers,			(,		20
1984 ⁹	34	2	30 (88)	10 (29)	>12.0
Samples and Binder,			(,	(=0)	12.0
1985 ¹⁰	76	11	63 (83)	40 (53)	23.0
Busin and coworkers,			(55)	(00)	20.0
198711	27	0	24 (89)	5 (19)	13.0
Overall	356	19	314 (88)	119 (33)	16.8

cases in the newer series make comparisons difficult.

In the older series involving anterior chamber and iris-fixated lenses (Table 2), the percentage of grafts that remained clear averaged 88% (314 of 356) with a range from 81% (21 of 26)8 to 95% (18 of 19).3 Average follow-up was 16.8 months (range, 12 to 24.5 months). Overall, 33% (119 of 356) of the eyes achieved a

visual acuity of 20/40 or better; the range among the studies was from 16% (three of 19)³ to 53% (40 of 76). Waltman⁴ suggested that the three most common causes for poor visual acuity after corneal transplantation for pseudophakic bullous keratopathy are cystoid macular edema, graft failure, and glaucoma.

Our results showed eight of 20 patients (40%) achieved a visual acuity of 20/40 or better,

TABLE 3
RESULTS OF PSEUDOPHAKIC BULLOUS KERATOPATHY ASSOCIATED WITH POSTERIOR CHAMBER INTRAOCULAR LENSES IN FOUR SERIES

INVESTIGATORS, YEAR	NO. OF EYES	AVERAGE TIME BETWEEN SURGERIES (MOS)	VI ACUITY	. WITH SUAL Y OF 20/40 TTER (%)	С	O. OF LEAR FTS (%)	AVERAGE FOLLOW-UP (MOS)
Kozarsky and coworkers,							
1984 ⁸	4	8.5	3	(75)	4	(100)	19.3
Schanzlin and coworkers,				(/		(,	10.0
1984 ⁹	2	_	2	(100)	2	(100)	>12.0
Arentsen and coworkers,				, , ,		(,	12.0
198714	25	7.0	9	(36)	25	(100)	15.0
Present series	20	10.3	8	(40)	18	(90)	14.0
Overall	51	9.0	22		49	(96)	15.0

which is an improvement over 33% (119 of 356) reported in the older series, as well as the 36% (nine of 25) reported recently by Arentsen and associates¹⁴ involving only patients with pseudophakic bullous keratopathy in association with posterior chamber intraocular lenses. In our study, 18 (90%) of the 20 grafts were clear at an average follow-up time of 14 months. Graft failure (two cases), senile macular degeneration (one case), and wound infection (one case) accounted for four of the five patients with a final visual acuity worse than 20/80.

It has been well documented that pseudophakic bullous keratopathy occurs between two and 2.5 times sooner than aphakic bullous keratopathy.3,7,9 However, while patients with aphakic bullous keratopathy are relatively similar to one another, in that they are all aphakic, patients with pseudophakic bullous keratopathy are somewhat heterogeneous, in that they may have any one of three types of intraocular lenses, and this heterogeneity may be reflected in differing times of onset of corneal edema. Possible factors contributing to the onset of corneal edema in eyes with iris-fixated and anterior chamber lenses have been discussed elsewhere. 15-20 Of particular interest is the short time interval between cataract surgery and the onset of corneal edema seen in our series of eyes with posterior chamber lenses. In 17 (85%) of our 20 cases, the onset of corneal edema was noted either immediately after or within one day of surgery. This is consistent with the results recently reported by Arentsen and associates.14 Of their 25 cases of pseudophakic bullous keratopathy associated with posterior chamber implants, corneal edema developed in 17 cases (68%) immediately after surgery and in eight cases (32%) within six months.

Both anterior chamber and iris-fixated intraocular lenses appear to be associated with a later onset of corneal edema compared with posterior chamber intraocular lenses. Kozarsky and colleagues8 reported that four cases involving posterior chamber intraocular lenses had an average interval of 8.5 months between cataract surgery and penetrating keratoplasty. The average interval in several small subsets of patients with posterior chamber intraocular lenses (including this study) was nine months (Table 3). Champion and Green²¹ reported a subset of six cases with posterior chamber implants and an average interval of 10.3 months between surgeries. In contrast, the study of Kozarsky and associates⁸ described six cases with anterior chamber lenses and 16 with irisfixated implants that had average intervals between cataract surgery and penetrating keratoplasty of 28.5 and 38.4 months, respectively. Two other reported series involved eight cases with anterior chamber lenses and an average interval of 16.1 months between surgeries. Busin and associates, in a study of intraocular lens removal during penetrating keratoplasty for pseudophakic bullous keratopathy, reported an average period between intraocular lens insertion and removal of 23.9 months for a series of 27 cases involving 22 anterior chamber lenses but no posterior chamber implants.

Many factors may contribute to the development of corneal edema after cataract extraction with intraocular lens insertion, including diseased endothelium, trauma to the endothelium during the surgical procedure, increased intraocular pressure postoperatively, the use of a large volume of irrigating solution during the surgical procedure, persistent uveitis, and apposition of the intraocular lens to the cornea. 6,7,9 Whether or not the endothelium is abnormal, only operative trauma is consistent with the acute onset of corneal edema observed with posterior chamber implants. Operative trauma in all cataract surgery has been found to lead to an increase in both endothelial cell loss and pleomorphism.²² Although continued cell loss is believed to be minimized with posterior chamber intraocular lenses,12 endothelial cell dysfunction is still thought to be the most important determinant of corneal edema.23 It seems likely, therefore, that the rapid onset of corneal edema is the result of either increased surgical manipulation, a decreased functional reserve of the corneal endothelium, or both.24 Preexisting endothelial dystrophy may be present in up to 50% of corneas with pseudophakic bullous keratopathy.5 Lugo and associates25 examined 20 histologic specimens and found evidence of primary endothelial disease and abnormalities in Descemet's membrane in 67% of the specimens.

We believe that the apparent increase in corneal edema associated with posterior chamber intraocular lenses is the result of an increase in the proportion of posterior chamber lenses in use, but that these lenses are associated with a lower incidence of long-term complications in many patients who have preexisting endothelial disease. Penetrating keratoplasty is easily performed in this subgroup of patients who develop pseudophakic bullous keratopathy; during the removal of the patient's cornea there is little danger of damage to intraocular

structures. No additional surgery in the form of intraocular lens insertion and removal or vitrectomy has been necessary in any of our cases. It appears that, among those patients with posterior chamber intraocular lenses who develop pseudophakic bullous keratopathy, the visual results and the percentage of clear grafts are somewhat improved over earlier series involving corneal transplantation for pseudophakic bullous keratopathy in eyes with anterior chamber or iris-fixated intraocular lenses.

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Topical Imipenem Therapy of Aminoglycoside-Resistant Pseudomonas Keratitis in Rabbits

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We used a rabbit model of bacterial keratitis to assess in vivo efficacy of topical imipenem, a highly potent β-lactam antibiotic with an unusually broad spectrum of activity, including aminoglycoside-resistant Pseudomonas aeruginosa. Albino rabbits received intrastromal injections of 5 × 10² organisms of an aminoglycoside-resistant strain of P. aeruginosa. At five hours postinoculation, imipenem (5 mg/ml) therapy was initiated using one drop per 30 minutes for 12 hours. Corneal tissue was then excised for colony forming unit counts. Imipenem was highly effective in reducing colony forming unit counts to zero in comparison to 4.1 × 105 organisms for untreated controls. A second regimen beginning 24 hours postinoculation of one drop per hour for 24 hours was also successful in significantly reducing colony forming units vs controls (P < .05). These data suggest that topical imipenem may have clinical applicability in the treatment of P. aeruginosa keratitis.

IMIPENEM is the first member of a new class of β -lactam antibiotics, the carbapenems. It has the broadest spectrum of any β -lactam antibiotic now in clinical use, including *Pseudomonas* species and approximately 99% of all bacterial isolates. The spectrum of activity includes most clinically important bacterial species and isolates resistant to most other agents. The β -lactam ring of imipenem is highly resistant to β -lactamases and this partially accounts for its high potency.

Although imipenem has been developed for parenteral use, we investigated its potential as a topical ophthalmic agent in an experimental bacterial corneal ulcer model. *Pseudomonas aeruginosa* keratitis is an increasingly frequent and often severe ocular infection, especially among extended-wear contact lens patients.⁵⁻⁸ Recent studies have indicated increased resistance of *P. aeruginosa* against conventional agents, including aminoglycosides.^{9,10} We studied the efficacy of topical imipenem in a rabbit model of aminoglycoside-resistant *Pseudomonas* keratitis.

Material and Methods

Penetration studies—We performed a pilot study to determine the aqueous humor penetration of topically applied imipenem. Twenty eyes of ten albino rabbits were divided into two groups. In the first five rabbits, imipenem (1 mg/ml) was topically applied every five minutes for a total of six doses. The second five rabbits received identical concentrations of imipenem at 30-minute intervals for a total of six doses. Samples of aqueous humor were obtained by anterior chamber paracentesis at intervals of 30 and 90 minutes after the last dose. A separate experimental trial with the corneal epithelium debrided at the onset was performed in the same fashion.

Imipenem aqueous humor samples were assayed by an agar well diffusion assay, 11 using 2 ml of a 1:100 dilution of *Bacillus subtilis* spore suspension (Difco Laboratories, Detroit, Michigan) and 23 ml of Antibiotic Medium 1 (Difco Laboratories) for each 150-mm polystyrene petri plate.

Standards and controls were prepared using N-formimidoyl thienamycin monohydrate standard powder, which was reconstituted in 0.01 M phosphate buffer, pH 7.0, and diluted in normal saline (0.85%) to yield standard concentrations of 0.4, 0.8, 1.6, 3.2, and 6.4 µg/ml. A control solution containing 2 µg/ml of imi-

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penem was prepared in the same manner. Standards and controls were aliquoted, stored at -70 C, and thawed on the day of use.

Five-microliter samples of standard, control, or aqueous humor were placed in a 3-mm well in the bioassay plate. Standards were run in duplicate; control and experimental samples were run in triplicate for each plate. The plates were incubated overnight at 37 C and the zones of inhibition measured. Aqueous humor concentrations were determined from plotting the log of the standard concentrations vs zone diameters (mm). Standard curve coefficients ranged from 0.990 to 1.000 and coefficients of variation for the 2.0-μg/ml imipenem control ranged from 5.2% to 8.1%.

Experimental model of Pseudomonas keratitis— We selected a strain of P. aeruginosa with demonstrated in vitro resistance to aminoglycosides (Table). Ten microliters of a suspension of 5×10^4 organisms was injected intrastromally and centrally into 12 rabbit corneas. Pilot studies showed that moderate keratitis was clinically evident by four hours postinoculation and severe keratitis consistently present by 24 hours. Rabbits were anesthetized with an intramuscular ketamine hydrochloride/xylazine mixture and topical proparacaine hydrochloride. Injections were administered under an operating microscope through a 30-gauge needle on a 100-µl syringe. The infections were allowed to proceed for five hours before initiation of antibiotic therapy.

TABLE

ANTIBIOTIC MINIMAL INHIBITORY CONCENTRATIONS
OF PSEUDOMONAS AERUGINOSA STRAIN 4N3422

ANTIBIOTIC	MINIMAL INHIBITORY CONCENTRATION (μG/ML)
Imipenem	1
Gentamicin	> 8
Tobramycin	> 8
Amikacin	8
Ticarcillin	32
Piperacillin	< 8
Ceftazidime	1
Ciprofloxacin	< 0.125
Cefotaxime	32
Cefoxitin	>32
Ceftriaxone	16
Cefuroxime	>32

The rabbits were then randomly divided into two groups and given imipenem (5 mg/ml) or normal saline topically. The imipenem concentration of 5 mg/ml is near the maximum solubility in water.⁴ In one experiment, we used a dosing regimen of one drop every 30 minutes for 12 hours. In a second experiment, we used a dosing regimen of one drop every hour for 24 hours.

After the last administered drop, the rabbits were killed and samples of aqueous humor were obtained by paracentesis for drug bioassay. Uniform corneal buttons were excised with an 8.5-mm sterile trephine. Corneal buttons were processed in a tissue homogenizer and serially diluted in normal saline. Each dilution was plated in duplicate onto trypticase soy with 5% sheep blood agar. Bacterial colony forming unit counts were then performed after overnight incubation at 37 C. Repeat antibiotic susceptibility testing was performed to monitor for possible antimicrobial resistance developing during therapy.

Results

Penetration studies—In both the intact epithelium and debrided epithelium studies, higher concentrations of imipenem were attained with the shorter dosing regimen (Fig. 1). For intact epithelium, the five-minute dosing regimen yielded a mean imipenem concentration of 2.1 $\pm 1.8 \,\mu\text{g/ml}$ at 30 minutes and $1.7 \pm 1.9 \,\mu\text{g/ml}$ at 90 minutes after the last dose, whereas the 30-minute dosing regimen yielded concentrations of $0.7 \pm 0.7 \,\mu\text{g/ml}$ and $0.4 \pm 0.5 \,\mu\text{g/ml}$, respectively. Similarly, in debrided epithelium, the five-minute dosing regimen yielded a mean imipenem concentration of 22.5 \pm 9.37 µg/ml at 30 minutes and 11.3 \pm 4.3 μ g/ml at 90 minutes after the last dose, whereas the 30-minute dosing regimen yielded concentrations of 10.6 ± 4.3 μ g/ml and 4.7 \pm 2.8 μ g/ml, respectively. Using these dosing regimens, therapeutic concentrations of imipenem in aqueous humor could only be attained in the presence of debrided epithelium.

Experimental model of Pseudomonas keratitis—In the 30-minute dosing experiment, the number of colony forming units of the untreated controls was 4.1×10^5 vs zero for the imipenem-treated eyes (Fig. 2). These results correlated with severe clinical keratitis noted in untreated controls and apparent resolution of

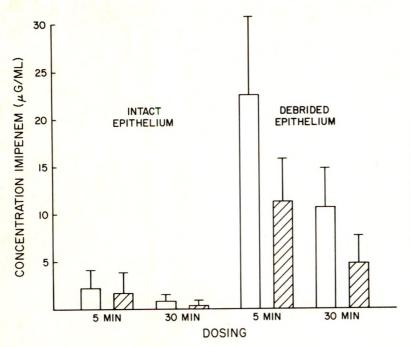


Fig. 1 (Sawusch and associates). Penetration of imipenem (1 mg/ml) into the aqueous humor after topical administration of six doses at five and 30-minute intervals on intact and debrided epithelium. Open bars, mean concentrations 30 minutes after the last dose; hatched bars, mean concentrations 90 minutes after the last dose.

keratitis in imipenem-treated eyes. Conversely, in the 60-minute dosing experiment, the number of colony forming units for the untreated controls was 3.4×10^5 vs 4.3×10^4 for imipenem-treated eyes (Fig. 2). Severe clinical

keratitis was noted in both treated and untreated groups. Repeat antibiotic susceptibility testing of corneal isolates after treatment did not demonstrate the emergence of antimicrobial resistance during therapy.

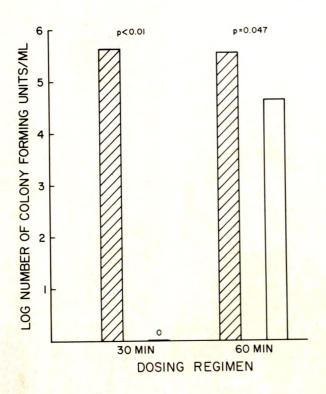


Fig. 2 (Sawusch and associates). Recovery of *P. aeruginosa* from infected rabbit corneas after topically administered normal saline (hatched bars) or imipenem, 5 mg/ml (open bars), using dosing regimens of one drop every 30 minutes for 12 hours or one drop every 60 minutes for 24 hours.

Discussion

Kropp and associates compiled the geometric mean minimal inhibitory concentrations (MIC₉₀) for imipenem against 31,702 isolates of 168 bacterial species. In this study, the MIC₉₀ (µg/ml) against common ocular pathogens were P. aeruginosa, 4.90; Staphylococcus aureus, <0.06; Staphylococcus epidermidis, <0.61; Streptococcus pneumoniae, <0.04; Haemophilus influenzae, 2.30; Neisseria gonorrhoeae, 0.30; Proteus vulgaris, 3.40; Escherichia coli, <0.31; and Klebsiella pneumoniae, 0.47. The highest MIC90 were against P. aeruginosa, yet they are relatively low in comparison with other antibiotics. The broad spectrum and potency of imipenem suggests potential use as monotherapy in clinical cases of keratitis with an equivocal Gram stain. Imipenem may also be synergistic with aminoglycosides against Pseudomonas and other common ocular pathogens.3

The penetration data in rabbits with intact corneal epithelium show subtherapeutic imipenem concentrations for *P. aeruginosa*, *H. influenzae*, and *Proteus vulgaris*, but concentrations in excess of the MIC₉₀ of other ocular pathogens. A uniform tenfold increase in penetration was noted in eyes with debrided epithelium, which may represent a better model of corneal ulceration. The half-life of imipenem in plasma is approximately one hour, ⁴ and our data suggest a similar half-life in aqueous humor. This relatively short half-life may partially explain the higher concentrations achieved by the shorter dosing regimen compared to the longer dosing regimen.

Pseudomonas keratitis is a common, potentially devastating ocular infection, especially among wearers of extended-wear soft contact lenses. 5-8 The ability of Pseudomonas organisms to bind to these contact lenses has been well demonstrated. Resistance of Pseudomonas strains to aminoglycosides9,10 can result in further corneal destruction because of delayed or ineffectual therapy. Roussel and colleagues10 reviewed 67 isolates of P. aeruginosa bacterial keratitis. Of these isolates, 59 (88%) were susceptible to gentamicin (MIC, <8 μg/ml), and 60 (89%) were susceptible to tobramycin (MIC, <8 μg/ml). Fifty-five of the 67 isolates were tested against amikacin and only 40 (73%) demonstrated susceptibility to this agent (MIC, <8 μg/ml). All four isolates which demonstrated resistance to both gentamicin and tobramycin

(MIC, >16 μ g/ml) were also resistant to amikacin (MIC, >16 μ g/ml).

The experimental model of keratitis demonstrated that imipenem was effective in reducing bacterial cell counts vs the saline controls. In the second study, where therapy was initiated 24 hours after inoculation, a much more florid keratitis was observed clinically. However, a statistically significant reduction in bacterial colony counts was observed in imipenemtreated eyes ($t_{22} = 2.15$, P = .047). This may be partially explained on the basis of microbial growth kinetics. Since β-lactam antibiotics inhibit cell wall synthesis, they are optimally effective during the early stages of an infection when the rate of multiplication is maximal. In the first keratitis experiment, where therapy was initiated five hours after inoculation, organisms were more likely to be in the exponential and vulnerable phase of growth. In the second experiment, where therapy was initiated 24 hours after inoculation, organisms were more likely to be in the less susceptible stationary growth phase. Therefore, the time of onset of therapy is critical in determining its success. This emphasizes the clinically recognized importance of early antibiotic therapy.

While topical imipenem caused no adverse effects during this study, there is need for further study concerning potential toxicities. A recent study showed no significant retinal toxicity in a rabbit model from therapeutic doses of imipenem in vitreous replacement fluid. In another study, intravitreal imipenem injections in a rabbit model were shown to produce mild retinal photoreceptor layer disruption only at doses exceeding 1 mg. Is

Imipenem is a highly potent β-lactam antibiotic with demonstrated effectiveness in an experimental model of *Pseudomonas aeruginosa* keratitis. With the high frequency and severity of *Pseudomonas* keratitis, especially in extended-wear contact lens patients, human therapeutic trials with topical imipenem are warranted.

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OPHTHALMIC MINIATURE

Real people look like luminous eggs when you see them. Nonpeople always look like people. That's what I meant when I said you cannot see an ally. The allies take different forms. They look like dogs, coyotes, birds, even tumbleweeds, or anything else. The only difference is that when you see them they look just like what they're pretending to be. Everything has its own way of being when you see. Just like men look like eggs, other things look like something else, but the allies can be seen only in the form they are portraying. That form is good enough to fool the eyes, our eyes, that is. A dog is never fooled, neither is a crow.

Carlos Castaneda, A Separate Reality New York, Pocket Books (A Division of Simon and Schuster), 1977, p. 40

Ocular Findings in Partial Trisomy 10q Syndrome

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We examined three siblings with partial trisomy 10q born to a mother carrying a balanced translocation between chromosomes 4 and 10. Our patients had many of the phenotypic abnormalities characteristic of this syndrome, and their chromosomal abnormality was confirmed by karyotypes of peripheral blood lymphocytes. Two ophthalmoscopic abnormalities not previously reported in this syndrome were noted in our patients. One child had bilateral enlarged, gray optic disks with elevated, blurred margins and distended retinal vessels. Another child had bilateral punctate yellow deposits scattered around the macula and optic disk.

Partial trisomy of the long or q arm of chromosome 10 was recognized as a distinct syndrome after the development of chromosome banding techniques. Between 1965 and 1971 the first reports were published by de Grouchy and Canet,1 Bühler and associates,2 and Kersey and associates,3 who each had patients with characteristic malformations and partial trisomy of a small C-group chromosome. As chromosome banding techniques developed, the patients described by Bühler and associates² and Kersey and associates³ were found to have trisomy of the q arm of chromosome 10.4 By 1974, Yunis and Sanchez⁵ recognized the striking phenotypic similarities among their patients and others known to have partial trisomy 10q6-9 and suggested that this represented a new chromosomal syndrome.

There have been few reports of ophthalmoscopic findings in partial trisomy 10q. We studied a family in which three of the four siblings showed partial trisomy 10q confirmed by chromosome banding (Fig. 1). Two previously un-

recognized ophthalmoscopic findings were noted in these patients.

Case Reports

Case 1

The oldest affected child was a 5½-lb full-term boy born to unrelated parents when his mother was 29 years old and his father was 28 years old. At 16 years of age, he was first examined by one of us (M.B.M.) for a "muscle problem" in his right eye noted by his parents since birth. The patient was mentally retarded and nonverbal, although he was able to cooperate with the examination. He had previously been found to have sensorineural hearing loss, hypotonia, and a neurogenic bladder. Unusual facial features included poor dentition, a highly arched palate, a wide nasal bridge, and an oval mouth.

Ophthalmic examination showed highly arched eyebrows, antimongoloid slant of the palpebral fissures, blepharoptosis, and epicanthus. Visual acuity was R.E.: 20/25-2 and L.E.: 20/20-1. Pupils were equal and round; direct and consensual light reflexes were intact. No afferent pupillary defect was noted. Ductions were full in both eyes, with an exotropia of 20 prism diopters. Results of slit-lamp examination of the cornea, anterior chamber, and lens were normal. Cycloplegic retinoscopy was found to be R.E.: $+2.50 +1.00 \times 90$ and L.E.: +2.75 +0.50 \times 90. Ophthalmoscopic examination demonstrated bilateral enlarged optic disks with elevated, poorly defined margins and a gray cast (Fig. 2). The retinal vessels, especially the veins, appeared dilated and tortuous. The macular areas appeared normal, and the overall retinal pigmentation was normal. Chromosome studies on peripheral blood lymphocytes showed 46, XY, -4, + der (4) t(4;10) (q35;q24) mat (Fig. 3).

Case 2

The second affected child, also a boy, was born without problems at full term weighing 5

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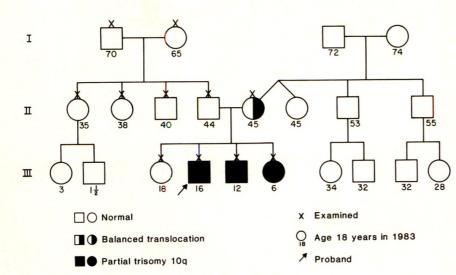


Fig. 1 (Neely and associates). Pedigree of family with partial trisomy 10q.

lbs. His mother was 33 and his father 32 years old at the time of this birth. This child was first seen at 12 years of age. He was also mentally retarded and nonverbal and had a history of seizure disorder, hypotonia, and sensorineural hearing loss. As did his brother, he had poor dentition, a highly arched palate, a wide nasal bridge, and an oval mouth.

Ophthalmic examination again showed fine, highly arched eyebrows, antimongoloid slant of the palpebral fissures, blepharoptosis, and

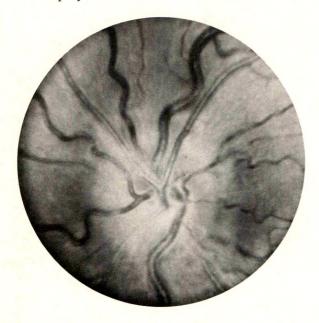


Fig. 2 (Neely and associates). Case 1. Appearance of the left optic disk and retinal vessels in the proband. The blurred disk margins and dilated retinal vessels were found bilaterally.

epicanthus. Visual acuity was R.E.: 20/20 and L.E.: 20/30. Pupils were normal, with intact light reflexes and no afferent pupillary defect. Ductions were full, with an exotropia at near of 20 prism diopters (Krimsky test). Results of slit-lamp examination of the anterior segments were normal. Cycloplegic refraction was plano bilaterally. Ophthalmoscopic examination showed normal optic disks with sharp margins. Retinal veins were slightly dilated and tortuous. Most strikingly, punctate yellow lesions were scattered diffusely around the disk and macula bilaterally (Fig. 4). Chromosomal studies on this child demonstrated the same abnormality as in his brother: 46, XY, -4, + der (4) t(4;10) (q35;q24) mat.

Case 3

The youngest affected child was a girl, born at full gestation and weighing 5 lbs. Her mother was 39 and her father 38 years old. This patient, 6 years old at the time of examination, was mentally retarded, but unlike her brothers, she was able to speak. As did her brothers, she had a sensorineural hearing loss, hypotonia, poor dentition, a highly arched palate, and a wide flattened nasal bridge.

Her ophthalmic examination showed fine, highly arched eyebrows, antimongoloid slant of the palpebral fissures, blepharoptosis, and epicanthus (Fig. 5). Visual acuity was 20/30 in both eyes. Pupils and pupillary reflexes were normal. Results of slit-lamp examination of the anterior segments were normal. Cycloplegic refraction was +2.50 bilaterally. Ophthalmoscopy demonstrated slight pallor of the optic disks but was otherwise normal. No abnormal

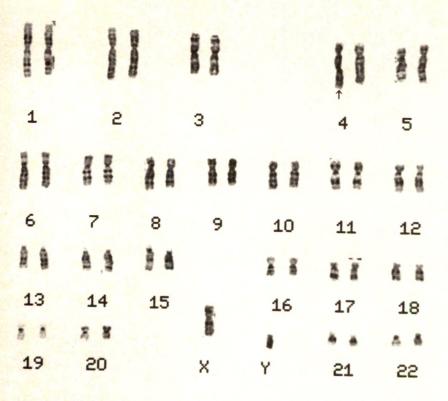


Fig. 3 (Neely and associates). Case 1. Karyotype of proband demonstrating an abnormal chromosome 4 (arrow) carrying a translocated segment corresponding to the distal q arm of chromosome 10. The patient also has two normal copies of chromosome 10 and is, therefore, trisomic for the distal q arm of chromosome 10: 46, XY, -4 + der (4) t(4;10) (q35;q24) mat.

pigmentation was seen. Chromosome studies showed the same abnormality as in her brothers: 46, XX, -4, + der (4) t(4;10) (q35;q24) mat.

Fig. 4 (Neely and associates). Case 2. Posterior pole of right eye in the proband's brother showing sharply demarcated punctate yellow deposits scattered about the macula and disk. The left eye had a similar appearance.

Other Relatives

Both parents were phenotypically normal as was their oldest child. The father's parents and siblings were examined and were also normal. By the mother's report, her family was normal although they were not available for examination. Chromosome studies were performed on peripheral blood lymphocytes of the proband, his siblings, and his parents, but on no other family members. Karyotypes for the proband and his two abnormal siblings are given above. The father and eldest sibling had normal karyo-



Fig. 5 (Neely and associates). Case 3. The youngest sister of the proband who shows features typical of partial trisomy 10q including arched eyebrows, antimongoloid slant of the palpebral fissures, blepharoptosis (not evident here because of brow lift), and epicanthus.

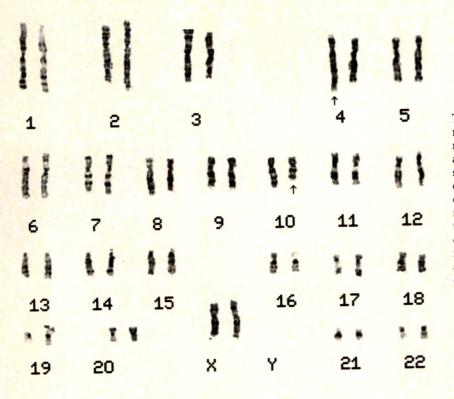


Fig. 6 (Neely and associates). The mother's karyotype. Arrows point out the abnormal members of chromosome pairs 4 and 10. The abnormal chromosome 4 carries the distal q arm of chromosome 10 annealed to its own q arm. The abnormal chromosome 10 shows a deletion of the 10q segments carried by chromosome 4. The mother thus is diploid for chromosome 10 and has a normal phenotype: 46, XX, t(4;10) (q35;q24).

types. The mother, however, had a balanced translocation: 46, XX, t(4;10) (q35;q24) (Fig. 6).

Discussion

The C group of chromosomes comprises seven pairs of medium-sized autosomes of which chromosome 10 is one of the smallest.⁷ Early reports described a number of phenotypes under the heading "trisomies C" because of difficulties in identifying with certainty the individual members of group C.¹⁰ With the application of chromosome banding techniques to this problem in the early 1970s,¹¹ chromosome 10 could be positively identified. Partial trisomy 10q could then be associated with specific systemic features.

Twenty-eight patients with partial trisomy 10q verified by chromosome banding have been described. Most cases appeared to have been caused by parental balanced translocations, most often between chromosome 10 and chromosomes 15, 17, and 18.4 Other chromosomes involved include 1, 2, 5, 11, 12, 14, 21, and 22. One patient acquired partial trisomy 10q from a meiotic recombination event involving a maternal chromosome 10 with a pericentric inver-

sion. 12 An additional but unpublished case mentioned by Yunis and Lewandowski⁴ appeared to have acquired the abnormality by a de novo translocation. The segments of 10q most frequently involved in the translocation have been q24—qter (16 patients) and q25—qter (six patients). One patient each has been trisomic for segments q22—qter and q23—qter. Less precise identification of the trisomic portion of chromosome 10q has been described in four other patients. The q arm of chromosome 10 generally translocates to a recipient chromosome that has minimal or no deletion. This may explain the great similarity among patients with this chromosomal abnormality.

Major systemic findings in partial trisomy 10q have been well characterized. About half of the reported patients have died at less than 1 year of age because of congenital heart defects or pulmonary disease. All but one reported patient have suffered severe mental and growth retardation. But one reported patient have suffered severe mental and growth retardation.

Characteristic facial features include microcephaly, prominent forehead, depressed nasal bridge, micrognathia, bow-shaped mouth and prominent upper lip, low-set ears, and, occasionally, cleft palate. Abnormalities of the hands and feet are also prominent and include overlapping fingers, camptodactyly, transverse

palmar creases, syndactyly of the toes, and deep plantar furrows. 4,14

Ocular findings most frequently reported include highly arched eyebrows, hypertelorism or pseudohypertelorism associated with epicanthus, antimongoloid slant, shortened palpebral fissures, microphthalmia, and blepharoptosis. Yunis and Sanchez⁵ as well as Klep-de Pater and colleagues¹⁵ reported cataracts in one patient each. Two patients with documented partial trisomy 10q have had sclerocornea. ¹⁵⁻¹⁷ Poor development of the anterior chamber, ¹⁷ nystagmus, ^{5,15} strabismus, ^{2,15} and distinct cutaneous vein markings on the upper eyelids ¹⁵ have also been noted.

Ophthalmoscopic findings in partial trisomy 10q have rarely been reported. Abnormalities described to date include replacement of the retina by fibrous tissue,⁵ pallor or blurring of the optic disks,^{9,17} and dilated retinal veins.¹² The patient described by Prosperi, Bernasconi, and Forabosco,¹⁸ the only one who underwent electroretinography, had diminished B-waves on the electroretinogram.

The family described here includes three siblings with partial trisomy 10q documented by study of Giemsa-banded chromosomes and is notable for two new ophthalmoscopic findings. First, the oldest affected child has unusual enlarged optic disks with a gray cast and elevated, poorly defined margins. As can be seen in Figure 2, these are reminiscent of, although not identical to, the morning glory syndrome. Second, the younger brother has normal optic disks, but both retinas show scattered, sharply demarcated, punctate yellow lesions concentrated in the posterior poles. No fluorescein angiography has been done, but these lesions appear to be near the level of the retinal pigment epithelium and may be similar to drusen. The youngest child has slight pallor of the optic disks, a finding that has been reported previously.

The mother of these children carries a balanced translocation involving 4q35 and the segment distal to 10q24. Her affected children are trisomic for the distal one third of the q arm of chromosome 10(q24→qter), and this has been the most frequently involved segment among the previously described patients. Past reports have shown chromosome 10 translocations involving 11 other autosomes, but this is a unique instance of chromosome 4 involvement.

Awareness of the systemic and ocular findings in cytogenetic syndromes should prompt appropriate chromosomal studies on the pa-

tient and the family. Information gained from these studies can be essential for genetic counseling.

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OPHTHALMIC MINIATURE

The old men studied magic in the flowers,
And human fortunes in astronomy,
And an omnipotence in chemistry,
Preferring things to names, for these were men,
Were unitarians of the united world,
And, wheresoever their clear eye-beams fell,
They caught the footsteps of the SAME. Our eyes
Are armed, but we are strangers to the stars...

Ralph Waldo Emerson, "Blight," 1847

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EDITORIAL

Counseling the Patient With a Posterior Uveal Melanoma

Jerry A. Shields

In recent years there has been considerable controversy regarding the best treatment of patients with malignant melanoma of the choroid and ciliary body. There is general agreement that the primary goal of treatment is the survival of the patient. Important secondary goals are preservation of vision and prevention of discomfort in the affected eye. The best method of achieving these objectives is not clearly established. Most authorities now agree that careful periodic observation is justified for small, melanocytic choroidal tumors which are not growing at a detectable rate. If the tumor grows, then some form of active treatment should be instituted.

See also p. 21.

There are strong advocates for primary enucleation and equally strong proponents of radiotherapy for the treatment of larger, progressive tumors. Proponents of irradiation do not

agree as to whether heavy ion radiotherapy^{5,6} or selected episcleral plaque radiotherapy⁷ is preferable. Advocates of enucleation do not agree as to whether preenucleation radiotherapy is effective in decreasing the incidence of metastasis. I am somewhat flexible in my recommendations and advise enucleation in some cases and radiotherapy, local tumor resection, or photocoagulation in others, depending upon the overall clinical findings.¹

Many of the world's experts on intraocular tumors attended the Second International Meeting on the Diagnosis and Management of Intraocular Tumors in Nyon, Switzerland, Nov. 23–27, 1987. There were many papers and discussions concerning the management of posterior uveal melanomas. The transactions of that meeting will be published but a few general points, which relate to counseling of affected

Ophthalmologists from several co

Ophthalmologists from several centers, where hundreds of patients have been treated

for posterior uveal melanomas, presented statistics comparing survival data on matched groups of patients treated by either radiotherapy or enucleation. Although there were no prospective randomized studies, the reports from Europe and the United States strongly implied no appreciable difference in survival between patients treated by enucleation and those treated by radiotherapy. 8,9 Increasing evidence suggests that there is no appreciable difference between heavy ion radiotherapy and plaque radiotherapy with respect to patient survival and local complications. 10-12 Additionally, there are no apparent differences in survival data contrasting different types of radioactive plaques.12 Other reports suggested that there is no appreciable benefit provided by radiotherapy prior to enucleation. 13,14

It is obvious that additional cases and longterm follow-up will be necessary to confirm these preliminary observations. Many authorities believe, however, that increasing evidence suggests that the type of therapy used for posterior uveal melanoma does not appear to alter the overall prognosis. There is general agreement that active treatment, rather than continued observation of a progressive tumor, provides the patient with a better chance of

cure.

I believe that before undergoing treatment for the uveal melanoma many patients have probably developed distant subclinical micrometastases. In these patients treatment directed only to the eye may not improve the chances of survival. Future research should be directed toward the detection of subclinical micrometastases and their management. Moreover, clinical trials designed to compare different types of treatment of posterior uveal melanomas must take into account the possibility of micrometastasis present before therapy.

This information must be considered when counseling a patient who has a posterior uveal melanoma. Such patients must be provided all information concerning alternative methods of treatment, their therapeutic complications, and survival rates. The discussion should avoid complex medical terminology that the patient may not clearly understand. The details of counseling will vary from patient to patient depending upon the clinical findings and the degree of patient apprehension. The following steps apply in most instances.

I first seat the patient and accompanying relatives in a quiet office and inform them that the eye contains a tumor. I review with them

the fundus drawings, fundus photographs, ultrasonograms, and any other studies and indicate that these findings support the clinical diagnosis of melanoma. They are told that melanomas within the eye are malignant, that they have the potential to metastasize outside the eye, and to cause death eventually in some patients. I stress that many patients are alive and well many years after diagnosis and treatment of the tumor.

The patient is then told that the management of uveal melanomas is controversial. Several years ago enucleation was the undisputed method of therapy, but some authorities suggest that enucleation may induce systemic dissemination of the tumor and have a detrimental effect on survival.² Other authorities question the accuracy of these observations and believe that enucleation is the most appropriate treatment in most cases.³

The patient is told that as a result of this controversy, several alternatives to enucleation have been suggested depending upon the size, location, and progression of the tumor as well as the patient's age, general health, and status of the fellow eye. These methods include periodic observation, photocoagulation, radiotherapy, and local resection of the tumor.

If the tumor is small and appears nonprogressive, initial observation may be advised. If the tumor is small but shows signs of progressive growth, then photocoagulation is considered. If the patient has an advanced melanoma in an eye for which there is little or no hope of retaining any useful vision, I believe that enucleation should be advised, rather than subjecting the patient to the possible external and visual complications of radiotherapy.

Most patients referred to me because of a uveal melanoma have a large tumor and the main therapeutic options are radiotherapy or enucleation.

I inform such patients as follows: (1) many physicians believe that the different types of radiotherapy and enucleation (with or without preenucleation radiotherapy) appear to have similar effects on survival; (2) a national, collaborative, prospective, randomized clinical trial is comparing the mortality after enucleation and plaque radiotherapy. If desired, the patient may enter such a study.

I tell the patient that several years ago we treated some melanomas larger than 20 mm in diameter and 10 mm in thickness with radiotherapy. Many patients with tumors of that size ultimately lost most or all of their vision in the

treated eye and experienced bothersome symptoms secondary to the radiotherapy. I now believe that enucleation should generally be recommended for these patients. This avoids exposing the patient to the potential external and visual complications of large amounts of radiotherapy. I inform the patient that some authorities recommend preenucleation radiotherapy but that recent studies suggest the survival rate is not improved. 13,14

If it seems likely that the eye with a choroidal melanoma can be saved with retention of useful vision by using irradiation, the patient is advised that radiotherapy is an alternative therapy. Generally, radiotherapy will cause regression of the tumor with retention of useful vision if the tumor is less than 12 mm in diameter and less than 8 mm in thickness. The patient may choose either heavy ion or an episcleral plaque after learning of the cost, technique, and potential complications.

It is difficult to make specific recommendations as to whether enucleation or radiotherapy is more advisable in patients in whom the melanoma is in a borderline range, for example, a melanoma that measures 14 × 14 mm in diameter and 9 mm in thickness. Such a patient should be encouraged to enroll in one of the national collaborative studies that compares the various therapeutic modalities. The patient should be informed as to the experience of the physicians participating in the collaborative study and the availability of an additional opinion by another physician with experience in the management of uveal melanomas.

The final decision as to the therapeutic method to be used should be made by the patient once the ophthalmologist has provided all available information regarding the various therapeutic choices. It has been my experience that the properly informed patient usually prefers radiotherapy and retention of the eye if I believe that any visual function can be preserved. A few patients will elect to have enucleation of the affected eye.

I believe that each patient with a posterior uveal melanoma must be thoroughly advised regarding the currently available information on the various treatment modalities and their techniques, costs, and potential complications. To do this, the consulting ophthalmologist must have a general knowledge of the results of recent studies concerning uveal melanomas and should advise the patient as to which form of treatment seems most applicable depending upon the clinical circumstances. Ultimately,

the patient should be allowed to make the final decision regarding a preference of therapy.

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LETTERS TO THE JOURNAL

Late Recurrence in Primary Orbital Rhabdomyosarcoma

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Orbital rhabdomyosarcoma is the most common primary orbital malignancy in children. Most recurrences following primary therapy occur within the first two years. Therefore in these, as well as in other pediatric solid tumors, we are encouraged by three-year relapse-free survival rates, because relapses after three years are rare.

A 20-year-old woman was seen in February 1981. She had had a painless enlarging mass in the left inferior orbit for two months. There had been progressive upward displacement of the left eye, which did not respond to a course of systemic corticosteroids given by her primary ophthalmologist. There was no pain, fever, or discharge. Visual acuity was R.E.: 20/15 and L.E.: 20/30. There was no afferent pupillary defect and the eyes were otherwise normal. The left eye was 2 to 3 mm displaced superiorly but motility was normal. Decreased retropulsion of the left eye was noted. An 11×24 -mm firm, nontender, nonmobile mass was palpable in the left inferior anterior orbit. Standardized left orbital echography demonstrated a compressible mass of low reflectivity in the inferior orbit that extended 5 mm posterior to the globe.

That evening, a left anterior orbitotomy was performed and the bulk of the tumor was resected. Histopathologic examination of the lesion disclosed a poorly differentiated embryonal rhabdomyosarcoma, confirmed by electron microscopic findings, with margins indicating residual tumor. She was treated with chemotherapy consisting of vincristine, dactinomycin, and cyclophosphamide for two years according to the Intergroup Rhabdomyosarcoma Study protocol. Administration of local irradiation was delayed until six months after tumor resection, at which point she received a total of 46 GyE.

She did well, with no evidence of tumor recurrence until January 1988, when she was again seen because of a one-month history of a left infraorbital mass associated with hypesthesia in the left infraorbital nerve distribution. A firm, nontender lesion, 10 × 20 mm, was palpable over the left maxilla in the region of the infraorbital foramen and was firmly attached to bone. Computed tomography showed a solid mass at the inferior aspect of the nasal complex and anterior wall of the maxillary sinus extending into the infraorbital foramen. No tumor was seen in the maxillary sinus or the orbit (Figure). A biopsy specimen of the lesion showed a poorly differentiated rhabdomyosarcoma with a histopathologic pattern similar to that of the original tumor.

Until the late 1960s, the treatment of choice for primary orbital rhabdomyosarcoma was exenteration, with the best reported three-year relapse-free survival rate being 32%. Reports of the efficacy of combined radiotherapy and chemotherapy were confirmed by the Inter-

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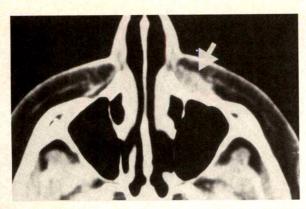


Figure (Chestler, Dortzbach, and Kronish). Axial computed tomography section through maxillary sinus at level of infraorbital foramen. Arrow points to recurrent rhabdomyosarcoma on anterior maxillary wall.

group Rhabdomyosarcoma Study, which showed a three-year survival rate of 93% in a total of 127 patients with localized orbital rhabdomyosarcoma.⁴

The reason that the prognosis of patients with primary orbital rhabdomyosarcoma is discussed in terms of three-year survival is that most recurrences occur within this time. Jones, Reese, and Krout³ reported 62 cases of primary orbital rhabdomyosarcoma, 51 of which had follow-up from six to 25 years. One recurrence occurred six years after exenteration in a patient who had not received adjuvant chemotherapy or radiotherapy, but otherwise all recurrences occurred within the first two years. In their series of 14 patients with localized primary orbital rhabdomyosarcoma, Sutow and coworkers1 found that six of their eight cases of recurrence or metastatic spread occurred within the first year after diagnosis, with one more in both the second and third years, but none thereafter with a minimum of five years of follow-up. In 16 patients with primary orbital rhabdomyosarcoma treated with combined radiation and chemotherapy with a mean followup of 49 months (range, 14 to 103 months), Kingston, McElwain, and Malpas⁵ saw no recurrences or deaths later than three years after diagnosis. Most recently, the Intergroup Rhabdomyosarcoma Study Committee4 reported that ten of 127 patients had relapses; of these, seven developed a recurrence within the orbit, and three in regional lymph nodes. The median follow-up of these 127 patients was six years,

with some observed for up to 14 years. All recurrences occurred within the first four years after treatment, which consisted of chemotherapy alone or in combination with either radiation or radiation and exenteration.

We believe the recurrence interval of six years ten months in our patient with primary orbital rhabdomyosarcoma is the longest reported in the literature and well beyond those previously reported following the improved treatment protocol that includes local irradiation, chemotherapy, or both. The site of recurrence in our patient is also of interest in that it suggests migration of tumor cells from the primary location in the inferior orbit through the infraorbital groove and canal to its site of relapse in the area of the infraorbital foramen. What role, if any, the delay in administration of local irradiation had in this patient's course is unclear.

We stress the importance of continued close follow-up of patients treated for primary orbital rhabdomyosarcoma in order to detect and treat late tumor recurrence. The most appropriate management of recurrent orbital rhabdomyosarcoma has not been well established, but must be individualized for each patient and might include surgical excision of tumor, local irradiation, or chemotherapy.

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Ocular Hazards of Rigid Blade Lawn Trimmers

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Rigid blade lawn trimmers consist of a rigid rotating blade on the end of a long handle. The blade, made of either rigid plastic or steel, is used to cut through heavy brush. We previously described a variety of injuries associated with nylon line lawn trimmers. We have encountered two cases of ocular trauma associated with rigid blade lawn trimmers, one of which occurred with the motor switched off.

Case 1

A 60-year-old man had just finished working with his rigid blade lawn trimmer and turned the machine off. He removed the safety glasses he had been wearing. The blade, which was spinning to a stop, struck the ground and threw a piece of metal into the man's left eye. There was immediate pain and decreased vision.

On initial examination, visual acuity in the left eye was reduced to counting fingers. Results of slit-lamp examination disclosed a corneal laceration with the iris incarcerated in the wound, and blood in the anterior chamber. A traumatic cataract was noted but the fundus could not be seen. Results of roentgenography studies of the orbit showed an intraocular metallic foreign body.

The patient underwent repair of his corneal laceration, pars plana lensectomy, vitrectomy, and removal of the intraocular foreign body. The patient subsequently developed a dense vitreous hemorrhage and underwent repeat vitrectomy and a scleral buckling procedure. Despite surgery he developed a blind painful eye and eventually required enucleation.

Case 2

A 58-year-old man was using his rigid blade lawn trimmer when he inadvertently struck a large piece of metal lying on the ground. He was wearing sunglasses, but not safety glasses, at the time of his accident. He noted irritation of his right eye along with minimal blurring of

vision. The next morning his symptoms had abated.

Approximately one month later the patient noted blurred vision. A traumatic cataract was diagnosed. The patient underwent cataract extraction and removal of a metallic foreign body with placement of an anterior chamber intraocular lens. Visual acuity reportedly improved to 20/25. He required two sessions of laser treatment for retinal holes. Approximately one year after his original injury, the patient noted a gradual decrease in vision and was referred for retinal examination.

On initial examination the patient's visual acuity was counting fingers in the right eye and 20/25 in the left eye. Results of slit-lamp examination disclosed normal eyelids, eyelashes, and conjunctiva. The cornea had a well-healed superior laceration and the anterior chamber intraocular lens was in place. Also noted in the anterior chamber were 3+ cells and flare and 2+ pigmented cells were present in the vitreous. Ophthalmoscopy showed a large inferior retinal detachment complicated by several fixed folds inferonasally and inferotemporally. There was an equatorial flap tear at the 5 o'clock meridian. He underwent a scleral buckling procedure with a lamellar dissection, pars plana vitrectomy, internal drainage of fluid, and gas-fluid exchange using 30% sulfur hexafluoride. Visual acuity improved from light perception to 20/200. The retina has remained attached and vision was stable eight months postoperatively.

The hazards of a rigid blade lawn trimmer when switched on are evident. The rigid blade spins freely on the end of a long handle. Only a portion of the blade is protectively housed, allowing for the cutting of weeds and brush. Ocular and generalized trauma from projectiles, as well as severe lacerations and amputations from direct contact with the rotating blade have been documented (Brush cutters, in Seasonal Safety Alert, U.S. Consumer Products Safety Commission, 1985).

The danger these machines present when switched off is not as readily apparent. The rigid blade continues to spin after the machine is turned off. The potential for injury by decelerating blades has been recognized in safety guidelines published by the government on lawn mower use (The product safety fact sheet. I. Power lawn mowers, U.S. Consumer Products Safety Commission, 1980). Because rigid blade trimmers are only partially covered in a protective housing, the decelerating blade has

an even greater chance than lawn mowers of throwing a projectile or coming into contact with the user.

Use of wraparound polycarbonate safety goggles is only one of the many safety measures that can help prevent the disabling ocular injuries that are possible with motorized lawn equipment.

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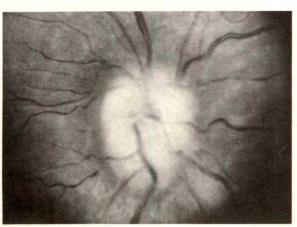
Optic Disk Drusen and Pseudotumor Cerebri

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Optic disk drusen (hyaline bodies) are deposits of material within the substance of the nerve head that occur in anatomically susceptible disks.¹ They are a common cause of pseudopapilledema (anomalous elevation of the optic disk without increased intracranial pressure),² and their presence may lead to a termination of



further diagnostic evaluation. However, optic disk drusen may coexist in a patient with increased intracranial pressure. Two cases of coexistent optic disk drusen and pseudotumor cerebri have previously been described, although their concurrence was presumed to have been due to chance. Herein we describe two additional patients with coexisting optic disk drusen and pseudotumor cerebri.

Case 1

A 34-year-old obese, black woman was referred for evaluation of headaches and frequent transient visual obscurations. The visual acuity was 20/20 in each eye and perimetry disclosed bilateral enlargement of the blind spots. Ophthalmoscopy disclosed bilateral papilledema with optic disk drusen (Figure). Fluorescein angiography showed autofluorescence of the drusen, with leakage and staining of the optic disk. A lumbar puncture showed an opening pressure of 370 mm Hg. Noncompliance with diet and intolerance to acetazolamide prompted therapy with furosemide, which was associated with a resolution of the visual obscurations and improvement of the papilledema. The optic disk drusen persisted.

Case 2

A 29-year-old black woman with a history of psychiatric disease and headaches had bilateral disk elevation. Perimetry disclosed enlarged blind spots bilaterally. The results of fluorescein angiography were consistent with optic disk drusen. One month later, reevaluation of worsening headaches disclosed bilateral disk edema with minimal retinal folds, venous engorgement, and loss of central cupping. Drusen were

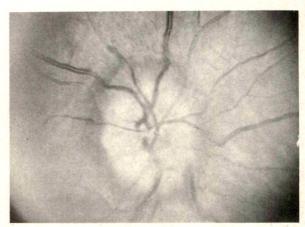


Figure (Reifler and Kaufman). Case 1. Fundus photographs from a patient with bilateral papilledema and optic disk drusen.

still visible at the peripheries of the optic disks and the visual fields were unchanged. The results of magnetic resonance imaging of the brain and orbits were normal. Lumbar puncture gave an opening pressure of 400 mm H₂O.

The pathogeneses of both papilledema and optic disk drusen have been ascribed to alterations of axoplasmic transport. ^{1,4} In chronic papilledema, drusen-like bodies may occur, only to disappear as either atrophy progresses or the intracranial pressure becomes normal. ⁵ Papilledema may be too short-lived to result in calcification of drusen. ¹ Conversely, the more dramatic axonal changes observed histologically in papilledema may be absent in the chronic, degenerative state characteristic of optic disk drusen. ⁴ How these factors and others might interact when pseudotumor cerebri and optic disk drusen coexist is still not known.

In our two cases, the coexistence of optic disk drusen and pseudotumor cerebri led to diagnostic confusion. In Case 1, a referring diagnosis of papilledema was considered doubtful by the finding of optic disk drusen. In Case 2, papilledema and pseudotumor cerebri developed subsequent to the diagnosis of optic disk drusen.

No statistically significant association of optic disk drusen with other ocular and neurologic disorders has been found with the possible exception of retinitis pigmentosa.² Despite our cases and those described previously, a statistical association of optic nerve head drusen and pseudotumor cerebri remains to be demonstrated. Careful study of a large number of patients with pseudotumor cerebri would help to support or refute any causal relationship between these two conditions.

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Optic Atrophy in Primary Oxalosis

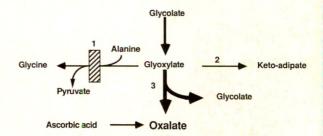
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Primary oxalosis is an inherited disorder of carbohydrate metabolism in which calcium oxalate crystals are deposited in diverse tissues. The most common form of the disease (type I) is caused by a deficiency of the enzyme alanine:glyoxylate aminotransferase (Fig. 1). Descriptions of ocular involvement in patients with primary oxalosis have concentrated on the striking retinal lesions seen in this disorder. We recently examined a patient with type I oxalosis in whom severe bilateral optic atrophy and retinal arteriolar attenuation accompanied the characteristic fundus abnormalities.

A 3-month-old boy was examined for failure to thrive and was found to have end-stage renal failure without hypertension. Oxalate deposition in the bones and kidneys, demonstrated radiographically and by biopsy, led to a diagnosis of primary oxalosis. The patient was



- 1. alanine : glyoxylate aminotransferase (pyridoxal)
- 2. 2- oxoglutarate : glyoxylate carboligase (thiamine)
- 3. lactate dehydrogenase

Fig. 1 (Small, Pollock, and Scheinman). The metabolic defect in primary oxalosis type I. The deficient enzyme is alanine:glyoxylate aminotransferase.

treated with intensive hemodialysis and underwent renal transplantation at 1 year of age. He has since been followed up for mild renal insufficiency secondary to recurrent disease and multiple orthopedic problems related to osteodystrophy.

An ocular examination performed at 7 months of age reportedly showed widespread yellow dots in each retina, bilateral darkly pigmented macular lesions, and bilateral optic atrophy. Flash visual-evoked responses were abnormal (P wave at 180 msec). When the patient was examined by us at 2 years of age, he was able to localize a 5-cm object at a distance of 2 feet with each eye. Roving nystagmus was present. Both pupils reacted to light. The anterior segments and intraocular pressures were normal. Scattered throughout the posterior pole and midperiphery of each retina were myriad bright yellow dots. A large, flat, charcoal-colored lesion with irregularly scalloped margins and overlying fibrous tissue occupied the macula in each eye. The retinal arterioles were markedly attenuated. Both optic disks were diffusely pale (Fig. 2).

Visual impairment in patients with primary oxalosis has been attributed to macular lesions consisting of calcium oxalate crystals surrounded by either annular or confluent areas of pig-

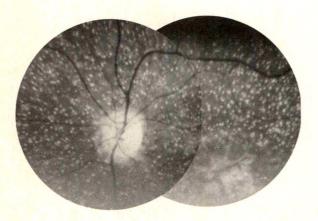


Fig. 2 (Small, Pollock, and Scheinman). Composite fundus photograph of our patient with primary oxalosis. Oxalate crystals are visible as scattered yellow dots. The large, charcoal-colored lesion in the macula represents reactive hyperplasia of the retinal pigment epithelium. Note the severe optic disk pallor and retinal arteriolar attenuation.

ment epithelial hyperplasia. Our patient had bilateral optic atrophy, a new finding in this disease. Although the characteristic macular lesions were also present, the atrophic appearance of the optic disks cannot be attributed to coexistent macular disease because the disk pallor was diffuse in each eye, not just temporal, and because a pathologic process confined to the pigment epithelium and outer retina should not produce loss of retinal ganglion cells. We believe that the optic atrophy in this case reflects widespread axonal loss from diffuse disease of the inner retina. This hypothesis is supported by the presence of concurrent severe retinal arteriolar attenuation and by a recent histopathologic study that demonstrated oxalate deposition in the inner retina as well as in the pigment epithelium.3 The pathogenetic mechanism may be toxic damage to the endothelium of retinal vessels with secondary loss of inner retinal elements. The toxic effects of oxalic acid on endothelial cells in vitro have been described. We suspect that these effects may occur in vivo as well. Another less likely cause of optic atrophy in patients with oxalosis is direct damage to nerve fibers from deposition of oxalate crystals in the optic nerve. Our findings indicate that involvement of the afferent visual system in patients with primary oxalosis may be more extensive than was previously believed and that visual compromise in this group of patients may not be caused solely by the associated maculopathy.

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Bright Light Stimuli as a Mask of Relative Afferent Pupillary Defects

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The ophthalmologist often uses the brightest available light source, including an indirect ophthalmoscope, to check for relative afferent pupillary defects. We have noted that relative afferent pupillary defects are often more obvious when testing with a relatively dim light. To explore this phenomenon, we determined the effect of bright light exposure (up to levels equivalent to an indirect ophthalmoscope set at high intensity) on the pupil over varying periods of time (Fig. 1). Bright light led to prolonged pupillary miosis of five minutes' duration. Reducing the intensity of the light stimulus to only 0.5 foot-candles (1/1,000 the intensity of full indirect ophthalmoscope exposure) for 10^{-3} seconds was required to abolish this prolonged miotic effect (Fig. 2). This work is in agreement with previous studies.1

The prolonged pupillary miosis may be caused by retina bleaching or by a more complex neural effect. Regardless, this prolonged miosis may obscure any relative pupil dilation in the alternate light stimulation test for relative afferent pupillary defects.

Additionally, an exponential decline in pu-

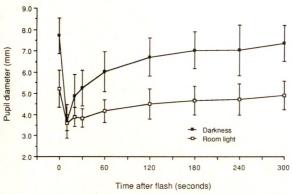


Fig. 1 (Borchert and Sadun). Exposure to bright light of 500 foot-candles for 10^{-3} seconds causes a prolonged pupillary miosis. The average pupil diameters in 14 normal subjects after exposure to a bright flash returns to the preflash baseline within five minutes in both light and dark adapted states (±1 S.D.).

pillary responsiveness occurs in the miotic state.² Stimulation with a bright light could put the pupil in this less responsive miotic position, making it difficult to assess subtle differences in pupillary excursion. For practical purposes it is this difference in pupillary excursion that allows for the detection of relative afferent pupillary defects.

There is another theoretical advantage in using a relatively dim light to detect subtle relative afferent pupillary defects. A close correlation exists between the size of the relative afferent pupillary defect as measured by neutral density filters, and the relative visual field 10ss.³ Although both physiologic and anatomic studies suggest that the density of pupillomotor ganglion cells may be slightly higher in the macula, they are well distributed throughout the retina.^{3,4} Hence small macular lesions, even though associated with severe loss of visual acuity, have small relative afferent pupillary defects, while optic nerve lesions that produce large peripheral field loss, even in the presence of good visual acuity, have larger relative afferent pupillary defects.

Optimum pupillary function reflects the characteristics of the area of the retina being stimulated. For example, the pupillary reactivity is lower with peripheral stimulation than with foveal stimulation, but the threshold for reactivity is also much lower. Additionally, the smaller peripheral responses are suppressed readily by adaptation to light. Therefore, the small relative afferent pupillary defect caused by an optic nerve lesion that results in a small

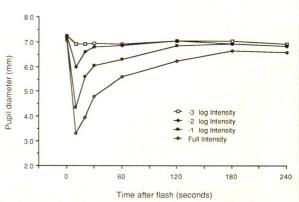


Fig. 2 (Borchert and Sadun). Reduction from full flash intensity of 500 foot-candles by log unit decrements for 10⁻³ seconds accelerates a return to the preflash pupil diameters. A one-thousandfold decrement in intensity is required to abolish the prolonged miotic effect.

area of peripheral field loss might be masked easily by the brisk foveal reflex from bright light. On the other hand, relative afferent pupillary defects associated with central field loss may be more prominent with a brighter stimulus. Perhaps a brighter stimulus should be used after failure to demonstrate a relative afferent pupillary defect with a dim stimulus in patients with poor visual acuity.

Further studies should be undertaken to assess the optimum stimulus intensity for detecting relative afferent pupillary defects, while considering the nature of the relative field loss. In the meantime, we recommend that the clinician begin a pupillary examination in a darkened room with a dim light stimulus, before proceeding to a brighter light source.

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Expulsive Choroidal Hemorrhage Following Suture Removal After Penetrating Keratoplasty

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Following postkeratoplasty suture removal, numerous complications that have been reported include wound dehiscence, bacterial endophthalmitis, and increased frequency of graft rejections. ¹⁻³ We encountered a case of delayed expulsive choroidal hemorrhage 16 months after keratoplasty following suture removal.

An 80-year-old man had severe ocular pain from bullous keratopathy. He previously had a cataract extraction with implantation of an Azar intraocular lens in 1983. He had hypertension with chronic bronchitis.

On ocular examination on Oct. 15, 1985, the visual acuity with correction was hand movements in the right eye and 20/60 in the left eye. Applanation tension was 21 mm Hg in the right eye and 23 mm Hg in the left eye. The right cornea had dense bullous keratopathy and the left cornea was clear. There was a well positioned Azar intraocular lens in the right anterior chamber. The iris was distorted superiorly. A 7.5-mm penetrating keratoplasty with an 8.0-mm donor button, anterior vitrectomy, intraocular lens exchange, and iridoplasty was performed on Jan. 17, 1986. The suturing technique used was 16 interrupted 10-0 nylon sutures at 90% depth buried on the recipient side.

The patient did well postoperatively but had mild glaucoma. The intraocular pressure postoperatively varied between 25 and 35 mm Hg. When seen on March 9, 1987, the corneal graft was clear and compact. The intraocular pressure was 28 mm Hg. The patient had a treatment regimen of fluorometholone, pilocarpine 4% ointment at bedtime, and timolol maleate 0.5% twice daily in the right eye.

The patient returned May 12, 1987, for suture removal. His visual acuity at that time was 20/400. The intraocular pressure was 25 mm Hg and the sutures were removed according to a previously described method.4 A large wound gap was immediately noted temporally between the 2 and 4 o'clock meridians. The chamber was still formed and deep. The patient was told another small operation was necessary to resuture the area of weakness. The patient's wife fainted and was taken out of the office in a wheelchair and rushed to the hospital emergency room, where it was determined she had a myocardial infarction. The patient was admitted two hours later. A nurse called stating the patient had a bloody drainage from his right eye and had a hypertensive crisis at that time. The patient was seen ten minutes after the telephone call and was found to have an expul-

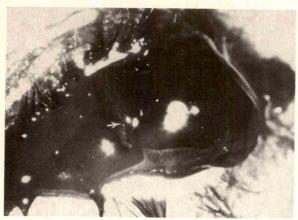


Figure (Perry and Donnenfeld). External photograph showing extensive expulsive choroidal hemorrhage with corneal button almost completely lost (arrow).

sive choroidal hemorrhage (Figure). The patient had an evisceration, and suffered a myocardial infarction in the recovery room.

The presence of glaucoma and a history of hypertension in an elderly patient is the most frequently encountered clinical manifestation of expulsive choroidal hemorrhage after keratoplasty. 5 That this patient had a hypertensive crisis just before his expulsive hemorrhage appears to have contributed directly toward this event, together with a long history of glaucoma in an eye with multiple surgical procedures that had just become relatively hypotonic. Most expulsive hemorrhages after keratoplasty are intraoperative and we believe our case is unique in that it occurred so far into the postsurgical period.⁵ In retrospect, we believe that resuturing should have been done immediately in the office under topical anesthesia, a procedure we currently use.

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Histopathologic Findings After Nd:YAG Transscleral Cyclophotocoagulation

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Glaucoma patients resistant to conventional medical and surgical therapy have been treated with a variety of cyclodestructive procedures. 1 In recent years, this approach has included the neodymium: YAG (Nd: YAG) laser, which has used for transscleral cyclophotocoagulation.² Fankhauser and coworkers³ noted that it is difficult to predict the degree of ciliary process destruction after Nd:YAG laser treatment and also expressed concern about possible damage to adjacent ocular tissues. Herein we report the histopathologic findings after Nd:YAG transscleral cyclophotocoagulation in one case.

The patient was a 51-year-old woman who had been referred to the glaucoma service for evaluation of unilateral glaucoma unresponsive to medical therapy. Iridocorneal endothelial syndrome of the Cogan-Reese (iris-nevus) type was diagnosed. Two trabeculectomies and a revision of the second trabeculectomy were performed over the next six years with only transient control of intraocular pressure. Visual acuity in the affected eye gradually decreased from 20/25 to hand motions despite aggressive medical and surgical therapy. The patient did not desire further filtering surgery. She elected to undergo Nd:YAG transscleral cyclophotocoagulation, which was performed 18 months after her most recent trabeculectomy. Treatment consisted of 35 single-pulse bursts of 3.44 to 3.49 J/pulse. The offset was 9 and the duration was 20 msec. No lens was used. All treat-

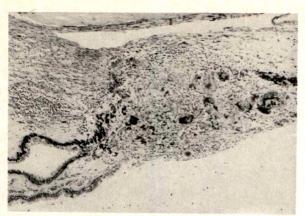


Fig. 1 (Shields and associates). There is disruption of the architecture of the ciliary body and ciliary epithelium with a granulomatous inflammation (hematoxylin and eosin, \times 100).

ments were aimed approximately 2 mm behind the corneoscleral limbus and perpendicular to the scleral surface. Postoperatively the eye became hypotonous, and the blind, painful eye was enucleated 70 days after Nd:YAG cyclophotocoagulation.

Histologic examination of the eye demonstrated endothelialization of the anterior chamber angle and iris, consistent with an iridocorneal endothelial syndrome. Extensive anterior and posterior synechiae were present. The ciliary body demonstrated areas of pigment disruption, loss of normal architecture, and granulomatous inflammation with prominent eosinophils (Figs. 1 and 2). Hyalinization of the ciliary processes was commensurate with the patient's age. The adjacent ocular tissues were normal, including the lens, retina, and sclera.

In the rabbit, Nd:YAG transscleral cyclophotocoagulation produces early depigmentation of the ciliary epithelium and late fibrosis and pigment dispersion in the ciliary body.3 Similarly, cryotherapy and diathermy produce early hemorrhagic necrosis of the ciliary pigment epithelium, with late ciliary body pigment disruption and fibrosis. Additionally, diathermy causes scleral necrosis at treatment sites.4 The reaction to cyclocryotherapy is similar in human and rabbit eyes. 5 No granulomatous ocular inflammation is seen after cyclocryotherapy in either humans or rabbits. In contrast, as we have described, Nd:YAG transscleral cyclophotocoagulation in one human eye produced the unusual finding of granulomatous inflammation. This may have been a foreign body reaction to the dispersed pigment

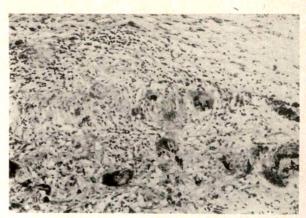


Fig. 2 (Shields and associates). Clusters of epithelioid cells with pigment phagocytosis are seen in the ciliary body (hematoxylin and eosin, \times 400).

in the ciliary body, but a similar reaction has not been seen with cyclocryotherapy or diathermy, which also cause pigment dispersion. This patient also had a history of the iridocorneal endothelial syndrome with previous filtering surgery, but neither of these conditions are associated with granulomatous inflammation. Since the inflammation was confined to the ciliary body, we have concluded that the changes were associated with the Nd:YAG cyclophotocoagulation. Based on this one case, it would appear that Nd:YAG cyclophotocoagulation can be used successfully without damaging the overlying sclera. Both of these conclusions require confirmation in further studies.

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Cytomegalovirus Infection of the Conjunctiva in AIDS

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Cytomegalovirus is the most common ocular opportunistic infectious agent in patients with acquired immune deficiency syndrome (AIDS).¹ It causes a necrotizing retinopathy, but only rarely infects ocular tissues other than the retina.²,³ We present histopathologic and electron microscopic evidence of cytomegalovirus infection of the conjunctiva, which was confirmed by immunohistochemical staining.

A 29-year-old homosexual man with AIDS developed cytomegalovirus retinopathy in the right eye 18 months before death. A three-week trial of ganciclovir arrested progression of the disease; however, exacerbation occurred following termination of the drug, and vision was lost. Recurrent bouts of herpes simplex keratitis developed in the right eye, which were responsive to topical antiviral therapy. Pseudomonas was cultured from a corneal ulcer two weeks before death. Despite antibiotic therapy, perforation ensued. Because of uncontrolled pain and spread of infection, the right eye was enucleated. At no time during the protracted course of cytomegalovirus retinopathy was conjunctivitis clinically diagnosed or treated.

Histopathologic examination of the eye disclosed marked acute panophthalmitis and inflammation of adnexal tissues. The retina was totally destroyed but showed no evidence of active cytomegalovirus retinopathy. The conjunctiva was markedly edematous and acutely inflamed. Cytomegalic cells, rarely containing prominent intranuclear inclusions, were surrounding and migrating through the walls of dilated conjunctival vessels (Fig. 1). Immunohistochemical studies demonstrated positive staining for cytomegalovirus antigen, while staining for herpes simplex virus types I and II antigens was negative. Electron microscopy of

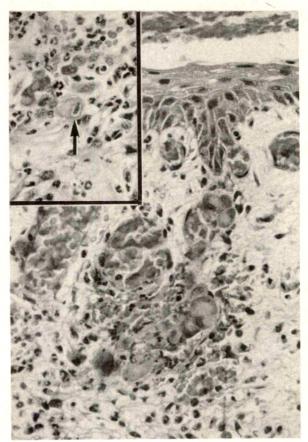


Fig. 1 (Brown and associates). A markedly inflamed and edematous conjunctiva contains numerous cytomegalic cells within and around conjunctival vessels (hematoxylin and eosin, \times 250). Inset demonstrates a cytomegalic cell within the stroma harboring an ''owl's eye'' intranuclear inclusion (arrow), characteristic of cytomegalovirus (hematoxylin and eosin, \times 250).

the conjunctival cytomegalic cells disclosed intranuclear and intracytoplasmic viral particles consistent with a herpes group virus, and intracytoplasmic membrane-bound homogeneous dense bodies characteristic of cytomegalovirus (Fig. 2).

Conjunctival involvement by cytomegalovirus has been reported in an acutely ill man with a previous history of infectious mononucleosis. The diagnosis was based on observation of cytopathic effect in human foreskin fibroblast cultures inoculated by a conjunctival swab, and on a concomitant increase in serum cytomegalovirus complement fixation titers; histopathologic confirmation was not obtained. Positive swab cultures may occur from cytomegalovirus in the tear fluid rather than an actual conjuncti-

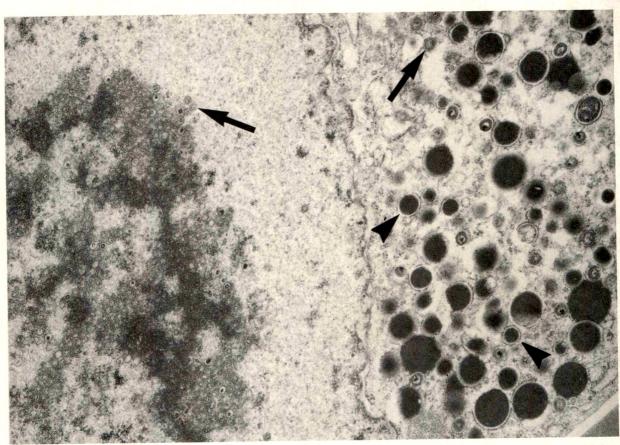


Fig. 2 (Brown and associates). Numerous intranuclear and intracytoplasmic herpes group viral particles (arrows) are present within an enlarged cell. Membrane-bound homogeneous dense bodies (arrowheads) are present in the cytoplasm ($\times 26,145$).

val infection. Cytomegalovirus has been isolated from the tear fluid of immunosuppressed patients without evidence of conjunctivitis, although some did demonstrate viremia, retinal involvement, or both.⁵

Electron microscopic confirmation of herpes virus particles in a random conjunctival biopsy specimen in an AIDS patient has been reported.³ The conjunctiva was unremarkable both clinically and histopathologically, and only on ultrastructural examination were viral particles observed. Herpes simplex pneumonia had been diagnosed and treated one month before conjunctival biopsy. Cytomegalovirus IgG index was increased at the time of ophthalmologic examination. Since cytomegalovirus and herpes simplex virions are indistinguishable by routine electron microscopic examination, further evaluation is necessary to clarify the specific type of virus present.

Our findings conclusively demonstrate active cytomegalovirus infection of the conjunctiva.

The pattern of involvement indicates a hematogenous dissemination of infected macrophages, an important means of multiorgan involvement. Shedding of the virus in the tears may be another source of conjunctival infection, and may also represent a contagious source for spread of the disease, although its importance in this regard is unknown. The relationship of conjunctival to retinal involvement must be assessed in order to determine the prognostic significance of conjunctival cytomegalovirus infection in individuals at risk for the development of AIDS.

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Keratitis Induced by Skin Polish

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Chemical keratitis resulting from the application of periocular cosmetics or from the use of aerosol sprays such as hair spray has been well documented. We studied a different form of keratitis that was produced by an abrasive cosmetic skin polish used around the eye and that strongly mimicked Thygeson's superficial punctate keratitis.

A 42-year-old woman complained of a chronic foreign body sensation in both eyes over a two-year period. Symptoms waxed and waned. Despite marked irritation and photophobia, the patient had no conjunctival discharge and occasional redness in the eye. She described no decrease in vision. The patient had been examined by many physicians and was treated with lubricants, topical antihistamines, and mild corticosteroids to no avail. The working diagnosis was Thygeson's superficial punctate keratitis.

Examination disclosed a visual acuity of 20/20 in each eye. The eyes were quiet and the conjunctivae were normal except for a mild superior tarsal papillary response. In the cornea of each eye were several glasslike, slightly irregularly shaped particles that appeared to be intraepithelial. These lesions did not move with blinking or with the tear film. The corneal stroma was normal (Figure). Corneal sensation



Figure (Mannis and Sandler). Minute glasslike beads embedded in the corneal epithelium.

was normal. The remaining results of the ocular examination were unremarkable. The referring ophthalmologist noted that similar lesions had been found on the superior tarsal conjunctiva as well as on the cornea and that the lesions could be "lifted off" with the tip of a needle. Careful questioning disclosed that the patient had been using a skin polishing agent on her face. She was aware that this polish was highly granular and that the instructions recommended that it not be used around the eyes. Examination of a smear of the material under the microscope disclosed myriads of glasslike particles.

This represents a case of multiple corneal and conjunctival foreign bodies from the periocular use of a facial cosmetic. The symptom complex including chronic, intense irritation in the absence of conjunctivitis with a waxing and waning course initially suggested the diagnosis of Thygeson's superficial punctate keratitis. However, close scrutiny of the corneal lesions at the slit lamp showed the tiny beads embedded in the epithelium rather than the more typical snowflake lesions of Thygeson's keratitis. Additionally, a trial of topical corticosteroids had no beneficial effects on the patient's symptoms.

This case underscores the importance of meticulous history-taking for the use of facial or periocular cosmetics that may adversely affect the ocular surface.

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Necrotizing Ring Ulcer of the Cornea Caused by Exogenous Listeria monocytogenes Serotype IV b Infection

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Listeria monocytogenes is a gram-positive, nonsporeforming, non-acid-fast, diphtheroidlike



Fig. 1 (Holbach, Bialasiewicz, and Boltze). Conjunctival chemosis and corneal ulcer (8 to 9 o'clock meridian) with stromal infiltration, large retrocorneal precipitates, and fibrin in the anterior chamber.

rod with a tumbling motility at room temperature, which may cause life-threatening granulomatous lesions in newborns and adults. Endophthalmitis caused by *L. monocytogenes* is extremely rare. ²⁻⁵

An 86-year-old woman who was diabetic had an exogenous L. monocytogenes infection with a corneal ring ulcer. She had had pain, redness, and decreased vision of the right eye for three weeks. The patient had no animal exposure or previous ocular diseases. Untreated diabetes mellitus had been known for ten years. Visual acuity was R.E.: 1/50 and L.E.: 20/30. Intraocular pressure was 16 mm Hg in both eyes. Corneal sensitivity was not decreased. Slit-lamp exof the right eye disclosed amination conjunctival chemosis, and a peripheral corneal ulcer in the 8 to 9 o'clock meridian with extensive stromal infiltration accompanied by a 2-mm hypopyon and fibrinous exudate in the anterior chamber, preventing visualization of the fundus (Fig. 1). The left eye had cortical cataract and choroidal sclerosis.

Laboratory studies of smears taken from the corneal ulcer disclosed *L. monocytogenes* serotype IV b. Despite systemic antibiotic therapy including 2 g of cefotiam three times a day and 500 mg of amikacin twice a day combined with gentamicin eyedrops every 15 minutes according to antibiotic susceptibility tests, intense flare and fibrinous reaction with a brown hypopyon as well as a secondary increase of intraocular pressure with extreme pain resulted in the patient's refusal to eat. The eye was subsequently enucleated on the l6th day after admission. Aqueous humor taken perioperatively did

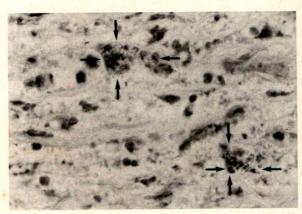


Fig. 2 (Holbach, Bialasiewicz, and Boltze). Positive reaction products (arrows) utilizing rabbit anti-Listeria-O-serum in sections of peripheral necrotizing corneal stroma (peroxidase-antiperoxidase, Boehmer's hematoxylin, ×1,200).

not grow bacteria. After removal of the globe the patient improved dramatically.

Histologic examination showed a necrotizing ring ulcer of the cornea with a dense cellular stromal infiltration, mainly composed of polymorphonuclear leukocytes, lymphocytes, plasma cells, and cellular debris. Evidence for the *Listeria* infection was found by immunoperoxidase staining using a rabbit anti-*Listeria*-Oserum (Fig. 2). A polymorphonuclear reaction could be seen in the anterior chamber as well as massive fibrinous exudate. The posterior segment of the eye did not show signs of inflammation.

Ocular complications of *L. monocytogenes* infections are known to pose therapeutic problems. None of the affected subjects described to date have achieved a better visual acuity than 20/200.²⁻⁵ Application of corticosteroids has not been proven beneficial. We propose immediate referral of patients with corneal ulcers and brown hypopyon, who live in the countryside, for thorough laboratory testing and early antibiotic therapy.

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Inferior Corneal Ulcers Associated With Palpebral Vernal Conjunctivitis

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Vernal conjunctivitis is a bilateral, often recurrent, seasonal inflammation of the conjunctiva that is characterized by a marked papillary reaction of the superior tarsal conjunctiva and limbal region. Vernal conjunctivitis may be associated with corneal complications that include nodular hyperplasia, pannus formation, punctate epithelial erosions, punctate epithelial keratitis, pseudogerontoxon, and keratoconus.1,2 Vernal ulcerative keratitis is seen with the palpebral form and is characterized by transversely oval corneal ulcers confined to the superior one half of the cornea.2-4 We treated two patients with palpebral vernal conjunctivitis and ulcerative keratitis involving not only the superior but also the inferior cornea.

Case 1

A 20-year-old man with a history of asthma complained of bilateral eye irritation, redness, and itching associated with swollen eyelids for six weeks. The visual acuity in both eyes was 20/30. Slit-lamp examination disclosed severe conjunctival hyperemia with giant papillae of the superior tarsal conjunctiva in both eyes. The right eye had a transversely oval ulcerative plaque in the superior cornea and a transversely oval stromal infiltrate associated with overlying epithelial defects and vascularization in the inferior cornea. The left eye had almost identical corneal findings. Giemsa stain of superior tarsal conjunctival scrapings showed numerous eosinophils. The patient was treated with topical fluorometholone 0.1% and cromolyn sodium 4%, one drop in each eye four times daily, with prompt resolution of symptoms in one day and epithelialization of the corneal ulcers within four days (Figs. 1 and 2).

Case 2

A 23-year-old man with a history of asthma and eczema complained of redness and irritation in both eyes for one month. The visual acuity was 20/200 in the right eye and 20/20 in the left eye. Slit-lamp examination of both eyes disclosed marked giant papillary changes of both upper and lower tarsal conjunctiva with the upper eyelids being worse than the lower eyelids. Both eyes showed conjunctival hyperemia and edema. The right cornea disclosed one superior horizontally oval ulcer and two smaller inferior ulcers, all three of which had plaque-like material at the bases. The left cornea was clear. The patient's symptoms responded to topical fluorometholone 0.1% every three hours in the right eye, but the ulcers failed to heal until a bandage lens was applied.

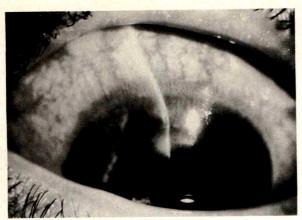


Fig. 1 (Shuler, Levenson, and Mondino). Case 1. Superior cornea of right eye shows residual scarring, thinning, and vascularization at site of previous ulcer.

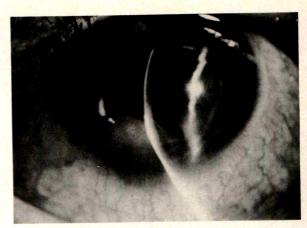


Fig. 2 (Shuler, Levenson, and Mondino). Case 1. Inferior cornea of right eye shows residual scarring and vascularization at site of previous ulcer.

The patient continued to have flare-ups of inflammation, which were controlled with low-dose topical corticosteroids and cromolyn sodium 4%. No further corneal breakdown occurred in either eye.

Corneal manifestations have been reported in as many as 50% of patients with palpebral vernal conjunctivitis.¹ Fortunately, the incidence of ulcerative keratitis in this disease is much lower, ranging from 3% to 4%.⁵ The vernal ulcer is characteristically described as transversely oval and located in the upper one half of the cornea.²⁻⁴ We are unaware of reports of vernal ulcers located in the inferior one half of the cornea. Three eyes of two of our patients with palpebral vernal conjunctivitis had ulcerative keratitis involving not only the superior but also the inferior cornea.

It has been postulated that the giant papillae of the upper tarsal conjunctiva may mechanically abrade the superior corneal epithelium during blinking, thereby initiating the ulcerative process. The superior papillae may initiate inferior corneal ulcers by the same mechanism. Only one of our two patients had a papillary reaction of the inferior palpebral conjunctiva, which may or may not have played a role in the formation of the inferior corneal ulcers.

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Foveal Retinoschisis Associated With Senile Retinoschisis in a Woman

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A 56-year-old woman reported a two-year history of "road signs looking like they were shot up with BBs." She denied nicotinic acid intake or difficulties with night, peripheral, or color vision. Her family history was noncontributory for visual problems. Visual acuity was 20/25 in each eye with a hyperopic astigmatic

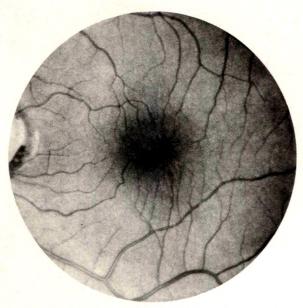


Fig. 1 (Han and associates). Fundus photograph of the left eye demonstrates inner retinal plications and cystoid changes radiating from the fovea. Similar changes were present in the right eye.

correction. Results of pupillary, motility, Amsler grid, and slit-lamp examinations disclosed no abnormalities. Ophthalmoscopy showed bilateral and nearly symmetric, fine, inner retinal plications and cystoid changes radiating from the fovea, which appeared characteristic of foveal retinoschisis (Fig. 1). The cystoid changes were limited to an area within 300 µm of the central fovea and appeared less elevated than those usually seen in early juvenile X-linked retinoschisis. There were no associated pigmentary or vascular abnormalities. Peripheral findings characteristic of senile retinoschisis, including fine, white dots and whitened vessels along the inner layer of the retina, were present for 360 degrees in both eyes. These changes were most prominent in the inferotemporal quadrants in both eyes and superonasally in the right eye, and were not associated with inner or outer layer holes. No peripheral pigmentary or vitreous abnormalities were detected. Fluorescein angiography showed small, faint areas of transmission hyperfluorescence within the foveal avascular zone of the left eye (Fig. 2). Results of Goldmann perimetry, Farnsworth panel D-15, photopic and scotopic electroretinography, and dark-adapted rod final thresholds at fixation and 20 degrees eccentrically were normal. Ophthalmic examinations of three of her four



Fig. 2 (Han and associates). Arteriovenous phase fluorescein angiogram of the left eye demonstrates faint areas of hyperfluorescence within the foveal avascular zone which faded in later phases of the angiogram. No leakage of fluorescein was seen in either eye.

daughters, aged 34, 35, and 37 years, demonstrated peripheral cystoid degeneration and normal foveas in all three and peripheral senile retinoschisis in the youngest.

Foveal retinoschisis in female patients is an unusual finding and has been associated with generalized rod-cone dystrophy,1 Goldmann-Favre disease,² and the XO and homozygous genotypes in juvenile X-linked retinoschisis.3,4 It has also been described with peripheral retinal pigmentary degeneration in a pedigree with autosomal dominant inheritance,5 and without peripheral fundus abnormalities in three sisters with presumed autosomal recessive inheritance.6 Except for the latter condition, it is unlikely that our case represents any of the above entities, given a family history that was not suggestive of X-linked inheritance, a normal cone and rod electroretinogram, and the absence of retinal pigmentary, vitreous, or lens abnormalities. Because our patient had peripheral retinoschisis and relatively normal visual function in her 50s, her condition also appears different from that of autosomal recessive inheritance reported by Lewis and associates,6 whose patients experienced a reduction of foveal function within the first two decades of life and had no peripheral schisis. We hypothesize that our patient may have manifested late findings of a dystrophic condition (one of her daughters also had peripheral retinoschisis), or that a degenerative process was responsible for both the foveal and the unusually extensive peripheral retinoschisis in this individual, the latter appearing clinically identical to senile peripheral retinoschisis.

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Use of Collagen Absorbable Hemostat in Dacryocystorhinostomy

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The control of operative and postoperative hemorrhage is a concern in dacryocystorhinostomy. It was previously common to have the patient's blood typed and cross-matched preoperatively for possible transfusion because of uncontrollable hemorrhage. Fortunately, a thorough understanding of the anatomy, an appropriate technique, topical and infiltrative vasoconstrictive medications, and local or hypotensive general anesthesia have made blood

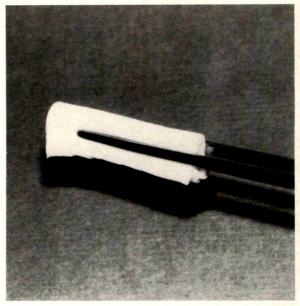


Figure (Dailey and Wobig). The collagen absorbable pad is pliable for easy intranasal application with bayonet forceps.

transfusion a thing of the past. However, moderate amounts of hemorrhage can still be a problem during surgery and in the postoperative period.

Intraoperatively, the hemorrhage can usually be controlled using the above mentioned measures combined with thermal or boviecautery. Despite excellent technique, bleeding may persist, however. This hampers the surgeon's view, and once the anterior flap of nasal mucosa is formed, the blood is free to drain into the patient's nose, and from there into the oropharynx, which can lead to serious problems in those patients whose airway is not protected by intubation.

Postoperatively, hemorrhage is usually prevented by placing a standard anterior pack using Vaseline gauze at the location of the newly created internal ostium. This pack is typically removed on the first postoperative day at which time significant bleeding can occur. The process of controlling this hemorrhage can be uncomfortable for the patient both physically and mentally as well as time consuming for the physician.

We have used a collagen absorbable hemostat (Instat, Johnson and Johnson) for hemostasis in our last 20 consecutive dacryocystorhinostomy procedures. The material is pliable and easily folded or cut with suture scissors to the appro-

priate size. We have found that one or two of the 1 × 2-inch pieces are satisfactory. The collagen can be placed into the wound or marsupialized ethmoid aircells with standard forceps, or at the tip of the middle turbinate with bayonet forceps (Figure). No anterior nasal pack is required to hold it in place. The material absorbs spontaneously. We have encountered no complications since we began using this absorbable hemostat about eight months ago. It is contraindicated in patients with a known bovine allergy.

We believe it has provided us with superior intraoperative hemostasis in cases where conventional means were time-consuming. We believe its biggest addition to lacrimal excretory surgery exists in the prevention of significant postoperative hemorrhage and it obviates the need to place an anterior pack in the nose of any of these patients. They seem more comfortable after surgery without the pack and all 20 have been dry on examination the first postoperative day. The internal nasal examination to confirm hemostasis is thus tolerated much better by the patients. No blood-soaked packs must be pulled out and we have not had to cauterize in a single patient. The time required for the first postoperative visit has been cut from between ten and 30 minutes to a routine five-minute visit in which most of the time is spent answering patient questions.

Correspondence

Correspondence concerning recent articles or other material published in The Journal should be submitted within six weeks of publication. Correspondence must be typed double-spaced, on 8½ × 11-inch bond paper with 1½-inch margins on all four sides and should be no more than two typewritten pages in length.

Every effort will be made to resolve controversies between the correspondents and the authors of the article before publication.

Unusual Central Chorioretinitis as the First Manifestation of Early Secondary Syphilis

EDITOR:

In the article "Unusual central chorioretinitis as the first manifestation of early secon-

dary syphilis," by E. C. de Souza, A. E. Jalkh, C. L. Trempe, S. Cunha, and C. L. Schepens (Am. J. Ophthalmol. 105:271, March 1988), no mention of the human immunodeficiency virus (HIV) serologic status is made in their three patients with this "peculiar type of central chorioretinitis" who, furthermore, had no history of a primary syphilitic process. In view of recent knowledge regarding the interaction between Treponema pallidum and HIV, this information is of great importance. One of their patients (Case 2) clearly belonged to a high risk group for HIV infection. The presence or absence of risk factors in the other two patients was not provided in the recorded data. However, a history of syphilis has been shown to be an epidemiologic risk factor for the development of AIDS.1 Ten of 30 patients with neurosyphilis had concomitant HIV infection in one study.2

Both the peculiarity of manifestation and the absence of history of primary syphilis in their patients may be explained readily if concurrent infection with HIV was present. Concomitant HIV infection appears to alter the natural course of syphilis, rendering the disease more aggressive, and with peculiar manifestations. Furthermore, it may accelerate the clinical course and shorten the latency period of syphilis.3 Neurosyphilitic manifestations that generally occur years after initial infection may occur after much shorter periods. Two of the patients reported by Johns, Tierney, and Felsenstein4 with neurosyphilis and concurrent HIV infection had no previous history of syphilis. A recent publication emphasized the importance of screening all patients infected with HIV for syphilis, and vice versa.3 Suspicion of concurrent AIDS should especially be aroused in the presence of peculiar or unusual manifestations of syphilis, as in the patients described by de Souza and associates. From a practical standpoint, a more aggressive approach to syphilis therapy may be needed in cases with concomitant HIV infection, as late syphilis relapses appear to be more likely in this setting.

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Reply

EDITOR:

We thank Dr. Hamed for his valid comments. In view of recent reports in the literature, a concomitant AIDS infection certainly should be considered when a diagnosis of syphilis is made. However, it is unlikely that the atypical nature of the clinical findings in our cases can be related to an associated infection with the HIV virus, because of the following: (1) our patients were healthy and remained symptom-free systemically, (2) the ocular involvement was unilateral and localized to the posterior pole, and (3) the improvement in response to treatment was dramatic. These observations indicate a less aggressive course than can be expected with a concomitant AIDS infection. Furthermore, our three cases were diagnosed and the patients were treated between 1980 and 1985 when HIV serology was not readily available on a routine basis.

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BOOK REVIEWS

Edited by H. Stanley Thompson, M.D.

Retinal Dystrophies and Degenerations. Edited by David A. Newsome. New York, Raven Press, 1988. 398 pages, index, illustrated. \$110

Reviewed by John R. Heckenlively Los Angeles, California

Because there has been a scarcity of texts on retinal degeneration and dystrophy in the last ten years, Newsome and collaborators have performed a real service in providing information on methods of evaluation and clinical approaches to a number of the common retinal dystrophies and disorders.

Chapter 1 immediately catches the reader's attention with practical guidelines for the clinical evaluation of the posterior segment by biomicroscopy; it is written by Andrew Packer and David Newsome. This chapter provides valuable methods and techniques for retinal examination using noncontact and corneal contact lenses. This theme is expanded by a broad description of techniques for clinical vitreoretinal evaluation by Sven-Erik Bursell and Martin Mainster, which covers ophthalmoscopy, fundus photography, video recording, ocular blood flow, indicator-dilution clearance measurement methods, fundus reflectometry, and vitreous fluorophotometry.

The beautifully illustrated chapters, Retinal Function and Physiological Studies and Cone Degeneration, by Richard Weleber and Alvin Eisner are clear and comprehensive. The chapter on cone degenerations covers many of the issues involved in sorting cone dystrophies from cone-rod dystrophies, but it would have been helped by the more generous use of color illustrations that was provided in other chapters.

Joann Boughman and Marcia Schwartz review principles of modern mendelian genetics and briefly cover population genetics, prenatal diagnosis, and linkage analysis, a powerful molecular biologic technique that allows localization of the gene site in specific chromosomes.

Vitreoretinal degenerations, juvenile retinoschisis, Goldmann-Favre syndrome, Wagner's disease, Stickler syndrome, familial exudative vitreoretinopathy, snowflake and lattice degeneration were broadly reviewed by Joel Schulman and Saul Merin, but a greater at-

tempt to sort out some of the contradictory features in reports was not made. In particular a recent study by Irene Maumenee in which she found that Wagner's disease appears to be a distinct entity from Stickler's syndrome and generally free of retinal detachment is not mentioned and would have helped the characterization of these two important diseases.

In the chapter on dominantly inherited drusen Bradley Jost has included almost any kind of posterior pole drusen, whether or not there was a family history. While age of onset is difficult to trace when it starts late in life, a more critical approach could have been taken as several diseases, including idiopathic retinal telangiectasia and fundus flavimaculatus, usually an autosomal recessive disease, appear to be represented in this chapter on dominant drusen. The chapter has useful advice, however, on the management of patients with drusen.

The chapter on juvenile hereditary macular dystrophies by Richard Lewis, which concentrates on forms of Leber's congenital amaurosis, congenital cone dysfunction, and Best's vitelliform dystrophy, is well illustrated.

Fundus flavimaculatus, one of the more common and least recognized retinal dystrophies, is reviewed by Paul Blacharski. Although the dark choroid effect is common in this entity, it was not noted that some progressive cone-rod dystrophies also have the dark choroid effect, and patients with macular lesions and posterior pole telangiectasia may require an electroretinogram to establish the correct diagnosis. Dr. Blacharski's chapter on pathologic myopia is particularly helpful since much of the material generally is not available to the reader, and the issues are well presented.

Retinitis pigmentosa, retinal pigment epithelial dystrophies, and Bruch's membrane degenerations are reviewed by Dr. Newsome. The progressive changes of retinitis pigmentosa on visual field examination are well illustrated, and management issues are appropriately addressed. Laser treatment of the macular edema of retinitis pigmentosa appears to be advocated, though this is highly controversial and not proven to be helpful compared to the natural course of the disease. The chapter on pigment epithelial dystrophies has a number of acquired conditions such as central serous retinopathy, evanescent white dot syndrome, and acute

posterior multifocal placoid pigment epitheliopathy and a section on hereditary retinitis pigmentosa syndromes that seem out of place in this chapter; some of this same material is duplicated in the chapter by Gabriele Lang and Irene Maumenee on retinal dystrophies associated with storage diseases, which has useful summaries on many rare disorders.

Choroideremia is reviewed by Clement McCulloch, who has extensive experience and has played a major role in defining this disease. Peripheral retinal degenerations, such as microcystic changes, degenerative retinoschisis, white without pressure, pavingstone and lattice degeneration are well described by James Augsburger.

Chapters by Andrew Schachat on toxic and nutritional retinopathies and retinopathy of prematurity summarize these conditions and are worthwhile additions to the text. Ocular toxoplasmosis, by Khalid Tabbara, is well illustrated and described.

This text is an important addition to the field of the retina. Although some selection and placement of material is uneven, this is nevertheless a superb collection not otherwise available from a single source. This book should be welcomed by those interested in retinal disease.

Oculoplastic, Orbital, and Reconstructive Surgery. Volume One, Eyelids. Edited by Albert Hornblass. Baltimore, Williams and Wilkins, 1988. 717 pages, index, illustrated. \$125

Reviewed by Bartley R. Frueh Ann Arbor, Michigan

This comprehensive view of eyelid anatomy, physiology, pathophysiology, pathology, and management is derived from the experience of 92 experts. The volume has the detail desired by someone with more than passing interest in the eyelids. The writing is, in general, of high quality. As with any multiauthored text, there is some degree of unevenness. The book is illustrated to the degree that this type of book demands, but with considerable variability in style of illustrations throughout. The drawings and photographs are beautifully reproduced.

Among the chapters noteworthy for not being commonly found in other texts are the

following: Chapter 9, The Psychological Implications of Ophthalmic Plastic Surgery; Chapter 17, Xeroderma Pigmentosum; Chapter 19, Contact Dermatitis; Chapter 20, Lipid Storage Diseases of the Eyelids; and Chapters 24 through 31, which cover in detail specific types of eyelid tumors. Beard's Chapter 14 on congenital blepharoptosis is a classic.

The book is organized into nine sections: an introduction, congenital and developmental anomalies, diseases of the eyelids, neoplastic diseases of the eyelids, disorders of the eyebrows and eyelashes, acquired eyelid malpositions, trauma, cosmetic ophthalmic plastic surgery, and reconstruction of the eyelids. This basic organization works well, except that Chapter 14 on congenital blepharoptosis is separated from Chapters 37 and 38 on acquired blepharoptosis. This excellent book would be still better if the redundancies and conflicts between chapters were eliminated or at least the variations cross-referenced.

There are a few errors or misstatements that are significant. In Chapter 3, surgery is recommended along Langer's lines. This would place vertical incisions on the nose, where they should be transverse. Borges' relaxed skin tension lines should have been recommended. In Chapter 43 on blepharospasm, the statement, "One study found no significant effect in over 100 patients," from facial nerve avulsion references a paper of mine. This statement is patently inaccurate. Chapter 44 on botulinum toxin injection, probably written four years ago, is so out of date as to be irrelevant.

I recommend that this book be on the shelf of all physicians who are especially interested in the fine points of the eyelid. Others who deal with the eyelid less frequently will probably wish to have this book available for consultation.

Books Received

Clinical Trials Supported by the National Eye Institute. National Institutes of Health (Publication 87-2910). Bethesda, National Eye Institute, 1987. Softcover, illustrated, 67 pages.

This booklet gives information on the 17 clinical trials now being supported by the Na-

tional Eye Institute. It lists all the individuals and institutions participating in each trial.

A free copy can be obtained from Ms. Judith Stein, Information Officer, National Eye Institute, National Institutes of Health, Building 31, Room 6A32, Bethesda, MD 20892.

Acute Anterior Uveitis, Ankylosing Spondylitis and HLA-B27, a thesis. By A. Mulock Houwer-Linssen. University of Amsterdam, The Netherlands, 1987. 156 pages.

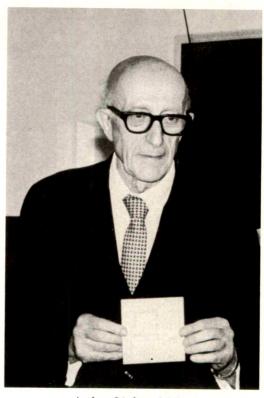
A detailed monograph on these two B27-related diseases.

Obituary

ARTHUR LINKSZ 1900–1988

One of the great teachers in ophthalmology, Arthur Linksz, died March 19, 1988. A profound thinker, a great scientist, a great lover of art and literature, a truly renaissance man passed into memory. It would be impossible to list all of Dr. Linksz's scientific and human achievements; only a few milestones can be described.

Dr. Linksz was born on June 23, 1900, in a part of Hungary that is now Czechoslovakia. In his younger years he wanted to be a poet. Political conditions after the First World War forced him to leave Hungary. He studied medicine in Prague, received his medical degree in Kiel, worked in Munich, and wanted to embark on a scientific university career. He moved back to Budapest and became a successful practitioner. He emigrated to the United States in 1939 and served as an instructor at Dartmouth Medical School with Prof. Alfred Bielschowsky and Prof. Hermann Burian. Immediately after his arrival in the United States he fell in love with the country and fell in love with the English language. He became an American citi-



Arthur Linksz, M.D. 1900–1988

zen in 1944. He published the "Physiology of the Eye, Volume I, Optics" in 1950, and "Physiology of the Eye, Volume II, Vision" in 1951. His book, "An Essay on Color Vision and Clinical Color Vision Tests," published in 1964, is a classic. "On Writing, Reading, and Dyslexia," published in 1973, is the story of his profound love affair with the English language. His Hungarian autobiography, "Visszanezck," was published in 1977, and its English translation, "Fighting the Third Death," in 1986. He delivered the Edward Jackson Memorial Lecture in 1958, closing it with a few minutes of testimony about his love of America and with the exclamation, "God Bless America!" He was a member of the American Ophthalmological Society and, of course, the Academy of Ophthalmology. He lectured and wrote extensively on topics of color vision, aniseikonia, vision screening, vision in the newborn, aphakia, and ophthalmodynamometry. "An Ophthalmologist Looks at Art" was published in 1980, a unique and marvelous book of a scientist who, at the same time, has profound understanding of artistic techniques and of the artists themselves. His

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thesis for the admission to the American Ophthalmological Society concerned the horopter. He also published a number of papers in German and in Hungarian concerning ophthalmic biochemical and clinical problems.

He was a very patient teacher, as his students at the Lancaster Course, and his residents at the Manhattan Eye-Ear-Nose Infirmary can testify. He was always a gentleman, a

friend, a teacher. In his later years he became a father model to many of us.

Generally a teacher lives as long as he lives in the memory of his own students, through his books, and his deeds. Arthur Linksz, the teacher, the friend, the advisor, will live much longer than that.

JOHN J. ALPAR

ABSTRACT DEPARTMENT

Edited by David Shoch, M.D.

Acta Medica Scandinavica

Plasma lipids and plasma lipoproteins in diabetics with and without proliferative retinopathy. Agardh, C. D., Agardh, E., Bauer, B., and Nilsson-Ehle, P. (Dept. Intern. Med., Univ. Hosp., S-221 85 Lund, Sweden). Acta Med. Scand. 223:165, 1988.

The authors examined the relationship of plasma lipids, plasma lipoproteins, and the duration of diabetes in type I diabetics with and without proliferative retinopathy. The duration of diabetes in the two groups was 12.2 ± 2.8 and 21.5 \pm 9.0 years, respectively (mean \pm S.D.; P < .01). Except for moderately decreased high-density lipoprotein levels, plasma lipid and lipoprotein concentrations were normal in both groups of patients. The levels of lipids and lipoproteins did not correlate with the duration of diabetes. Furthermore, no differences were seen between patients with and without proliferative retinopathy. Thus, plasma lipids and plasma lipoproteins did not play a major role in the development of diabetic proliferative retinopathy. (1 figure, 2 tables, 21 references)-David Shoch

Acta Ophthalmologica

Myopia and stature. Teikari, J. M. (Univ. Helsinki, Dept. Public Health, Haartmaninkatu 3, SF-00290 Helsinki, Finland). Acta Ophthalmol. 65:673, 1987.

In a study of the association between myopia and stature, the author first compared 187 myopic men and women with 603 nonmyopic subjects and then compared both monozygotic and dizygotic twins where one twin was myopic and the other was not. Both studies showed an association between height and myopia in men. The myopic men in general tended to be taller than the nonmyopic men. This association was not found among women. In the twin studies,

the male twin with myopia was taller than his nonmyopic twin at age 10, 15, and 20 years; among females there was no difference. (3 tables, 13 references)—David Shoch

Ocular hypertension. A prospective twentyyear follow-up study. Lundberg, L., Wettrell, K., and Linner, E. (Dept. Ophthalmol., Vegtergaarden, Albani torv, DK-5000 Odense, Denmark). Acta Ophthalmol. 65:705, 1987.

Of 41 patients with ocular hypertension who were followed up for 20 years, 14 developed glaucoma (34%). Of 38 control subjects who were normotensive at the onset of the study, two (5%) developed glaucoma. This difference was statistically significant. Mean intraocular pressure of the untreated ocular hypertensive patients was about 7 mm Hg higher than mean intraocular pressure in the control group. (2 figures, 15 references)—David Shoch

Two year electrophysiology follow-up in quinine amblyopia. Moloney, J. B. M., Hillery, M., and Fenton, M. (Res. Found., Eye and Ear Hosp., Adelaide Rd., Dublin 2, Ireland). Acta Ophthalmol. 65:731, 1987.

A 19-year-old girl presenting with quinine amblyopia had serial electrophysiology studies over a 2 year period. Visually evoked responses and the electro-oculogram were abolished early. By 2 months the VER and visual acuity had returned to normal. The electroretinogram, initially mildly subnormal, became virtually abolished by 2 months. No recovery in cone function took place. Of the rods 50% regained function with normal latency by 1 year, but receptor sensitivity did not return to normal until 2 years after ingestion. The electro-oculogram also recovered slowly over a 2 year period. This pattern suggests that quinine exerts a direct toxic effect on the cells of

the outer retina and pigment epithelium, as well as on the ganglion cells. (2 figures, 13 references)—Authors' abstract

British Journal of Dermatology

Immunofluorescent studies in ocular cicatricial pemphigoid. Leonard, J. N., Hobday, C. M., Haffenden, G. P., Griffiths, C. E. M., Powles, A. V., Wright, P., and Fry, L. (Dermatol. Dept., St. Mary's Hosp., Praed St., London W2 1NY, England). Br. J. Dermatol. 118:209, 1988.

Of 29 patients included in this study, 17 had cicatricial pemphigoid, five had pseudopemphigoid assumed to be the result of long-term use of topical antiglaucoma medications, and seven had a systemic or local disease with which scarring of the conjunctiva has been associated. Ten of 17 patients with cicatricial pemphigoid showed positive direct immunofluorescence compared to one of five patients with pseudopemphigoid and two of the seven patients with scarring associated with other diseases. Immunoglobulins against a basement membrane were found in seven of the patients with cicatricial pemphigoid, three patients with pseudopemphigoid, and two patients with cicatrizing conjunctivitis caused by other diseases. The results indicated that direct immunofluorescence was useful but not absolutely diagnostic for ocular cicatricial pemphigoid. The high incidence of circulating antibodies in the pseudopemphigoid group seemed to indicate that this disorder is immunologically related and is probably triggered by the use of medications. (2 figures, 5 tables, 21 references) —David Shoch

British Journal of Ophthalmology On the management of retained airgun pellets. A survey of 11 orbital cases. Jacobs, N. A., and

Morgan, L. H. (Dept. Ophthalmol., Charing Cross Hosp., Fulham Palace Rd., London W6 8RF, England). Br. J. Ophthalmol. 72:97, 1988.

In a review of 11 cases of retained lead airgun pellets in the orbit, particular attention was directed to possible mechanical effects and the hazard of lead toxicity. The duration of foreign body retention varied from one month to 26 years. All serum lead levels fell within the normal range of less the 300 μg/l. There was limitation of eye movement in two patients. Two eyes had been enucleated and two eyes were retained but disorganized. Six patients had a visual acuity of 6/12 or better and one patient had a visual acuity of 6/18. Surgical intervention is indicated only when there is mechanical disturbance or ocular motility associated with good visual function. (1 table, 20 references)—David Shoch

Histological appearances of the levator palpebrae superioris muscle in Marcus Gunn phenomenon. Lyness, R. W., Collin, J. R. O., Alexander, R. A., and Garner, A. (Inst. Ophthalmol., Univ. London, 17-25 Cayton St., London EC1V 9AT, England). Br. J. Ophthalmol. 72:104, 1988.

In 1883, Marcus Gunn described a case of unilateral congenital blepharoptosis affecting the left side. The salient features were contraction of the levator palpebrae muscle in association with the external pterygoid muscle, diminished tonic and active action of the muscle in its association with other muscles supplied by the third nerve, and imperfect relaxation of the muscle when the eyelids were gently closed.

In biopsy specimens from both eyelids of 12 patients undergoing bilateral eyebrow suspension to correct unilateral Marcus Gunn phenomenon, there were fewer fibers on the affected side in all patients compared to the normal side. Ten of 12 specimens of the clinically normal side showed fewer fibers than might be expected in a normal levator muscle. The levator muscles on both sides showed central accumulations of mitochrondia within individual muscle fibers. The findings suggest that the process underlying the Marcus Gunn phenomenon is a neurogenic atrophy with aberrant

reinnervation. It is a bilateral abnormality, with one side affected more severely than the other. The initiating pathologic process is probably located within the brainstem rather than being a peripheral lesion of the third nerve, and the initial lesion occurs in utero. (9 figures, 3 tables, 15 references)—David Shoch

Growth and contractility of cells from fibrocellular epiretinal membranes in primary tissue culture. Jiang, D. Y., Hiscott, P. S., Grierson, I., and McLeod, D. (Pathol. Dept., Inst. Ophthalmol., 17-25 Cayton St., London EC1V 9AT, England). Br. J. Ophthalmol. 72:116, 1988.

The authors grew cells from 37 of 53 specimens of epithelial retinal membranes obtained during vitrectomy. In general, the cells from membranes that were less than four months old grew more rapidly than cells from older membranes. Electron microscopy demonstrated prominent microfilaments in the cytoplasm of some of the cells and variable staining for actin. This study demonstrated that epithelial cells can contract and, since they act like smooth muscle cells, the authors speculated whether smooth muscle relaxants might have a role in treating epiretinal membrane contraction. (12 figures, 4 tables, 24 references)—David Shoch

Localising patterns of optic nerve hypoplasia.

Retina to occipital lobe. Novakovic, P., Taylor, D. S. I., and Hoyt, W. F. (Dept. Ophthalmol., Hosp. for Sick Children, Great Ormond St., London WC1N 3BG, England). Br. J. Ophthalmol. 72:176, 1988.

In six cases of optic nerve hypoplasia, one patient had a squint and macular colobomas, and a second patient had a squint and a classic unilateral hypoplasia with an associated afferent pupillary defect. The third patient had an afferent pupillary defect and a sharply defined altitudinal field defect with a hypoplasic upper half of the disk as well as a retinal nerve fiber layer defect superiorly. The fourth patient had

a nystagmus and a bitemporal field defect. A similar field defect was seen in the fifth patient who had seesaw nystagmus, indicating a suprasellar lesion. The sixth patient had a left homonymous hemianopsia and computed tomography showed a cyst of the right occipital pole. Thus, it would appear that optic nerve hypoplasia can be associated with lesions anywhere in the visual pathway. (6 figures, 54 references)—David Shoch

Blindness from quinine toxicity. Bacon, P., Spalton, D. J., and Smith, S. E. (Med. Eye Unit, St. Thomas's Hosp., London SE1 7EH, England). Br. J. Ophthalmol. 72:219, 1988.

In a patient with quinine toxicity, visual acuity was reduced to light perception in both eyes and the pupils were dilated and fixed. The retinas were edematous. A stellate ganglion block was performed on one side, which had no effect on the visual outcome. There was a gradual return of visual acuity to 20/20 in each eye, but the visual fields remained constricted. The pupillary responses remained poor, with both an afferent and efferent deficit. Four weeks later the electro-oculogram was reduced, and there was a loss of the B-wave in the electroretinogram and reduced flicker fusion. These results, in addition to the absence of any difference in recovery between the two eyes, showed that quinine exerts its toxic effect directly on the retina and that the resulting visual impairment is not the result of vascular changes. Stellate ganglion block was not advised for the treatment of quinine ocular toxicity. (4 figures, 1 table, 27 references)—David Shoch

Eye

Intraocular involvement of T and B cell lymphomas. Graham, E. (Med. Eye Unit, St. Thomas's Hosp., London 7EH SE1, England). Eye 1:691, 1987.

In six patients with this non-Hodgkin's lymphoma, ocular findings were generally noted in patients over age 55 years. Other common findings included bilaterality, constricted visual fields with reduced color vision, fine keratic precipitates, and large profuse vitreal cells. Fluorescein angiography showed pigment epithelial abnormalities and the response to corticosteroid therapy was poor. In patients with these findings, bone marrow examination, plasma protein and immunoglobulin study, and cerebrospinal fluid examination are indicated. (4 figures, 5 tables, 25 references)—David Shoch

Conjunctival incisions for trabeculectomy and their relationship to the type of bleb formation. A preliminary study. Agbeja, A. M., and Dutton, G. N. (Tennent Inst. of Ophthalmol., Univ. Glasgow, Western Infirm., Glasgow G11 6NT, Scotland). Eye 1:738, 1987.

Thirty glaucoma patients requiring trabeculectomy were randomly divided into three groups. Patients in one group received a fornixbased flap, in the second group a straight conjunctival incision was used to create a limbal-based flap, and in the third group a curved conjunctival incision was made extending to the corneoscleral limbus at either end of the flap. The blebs were classified as being either cystic or diffuse. In eight of ten patients with a fornix-based flap, a diffuse bleb was created. In the other two groups there were an equal number of cystic and diffuse blebs. The original vascular pattern was most likely to be retained with a fornix-based flap, whereas patients with a limbal-based flap frequently showed new vessel growth across the scar. (6 figures, 3 tables, 14 references)—David Shoch

Neurology

Neuro-ophthalmologic complications of cardiac catheterization. Kosmorsky, G., Hanson, M. R., and Tomsak, R. L. (Dept. Ophthalmol., Cleveland Clin. Found., 9500 Euclid Ave., Cleveland, OH 44106). Neurology 38:483, 1988.

In a review of 30,000 cardiac catheterizations over a five-year period, only ten patients had neuro-ophthalmologic complications. Eight of the ten patients had embolic phenomena and two showed migraine-type disorders. Eight patients recovered from their loss of visual acuity or visual field and one was lost to follow up. The tenth patient had a final visual acuity of 20/200. Although the incidence of these complications is small, the authors suggest frequent flushing of the catheter to reduce catheter embolism and perhaps to avoid the guide wires. Further, they believe that femoral catheterization has less risk than antecubital insertion. (1 figure, 1 table, 9 references)—David Shoch

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Science

The nasotemporal division in primate retina. The neural bases of macular sparing and splitting. Leventhal, A. G., Ault, S. J., and Vitek, D. J. (Dept. Anat., Univ. Utah School of Med., Salt Lake City, UT 84132). Science 240:66, 1988.

The authors injected horseradish peroxidase into the lateral geniculate nucleus and the superior colliculus of eight monkeys. Most of the foveal pit was located in temporal retina, with about a 0.5-degree range of densely packed, ispilaterally projecting cells circling the nasal side of the foveal pit. This distribution was not detected after injection of the superior colliculus. Their results indicated that ipsilaterally projecting cells in and around the fovea can generate 2 to 3 degrees of bilateral representation of the geniculocortical pathways. This finding is apparently true only of primates. Therefore, damage to the visual pathway in one hemisphere should result in foveal splitting in the eye ipsilateral to the lesion and foveal sparing in the eye contralateral to the lesion. Similar clinical findings have been reported. There appears to be a neural base for macular sparing of the splitting. (1 figure, 17 references)—David Shoch

Absence of TGF-β receptors and growth inhibitory responses in retinoblastoma cells. Kimchi, A., Wang, X. F., Weinberg, R. A., Cheifetz, S., and Massague, J. (Dept. Virol., Weizmann Inst. Sci., Rehovot 76110, Israel). Science 240:196, 1988.

Normal cells, including those of the retina, contain receptors for a substance called the transforming growth factor-beta, which inhibits cell division and unchecked cellular proliferation of cells. Some tumors also contain receptors for this substance. Cells that contain such receptors might be inhibited by treatment with transforming growth factor-beta. The authors applied this substance to retinoblastoma cells and found that it had no effect on DNA synthesis or cell division. They performed binding studies that demonstrated that the retinoblastoma cell lacks a receptor for the inhibiting

transforming growth factor-beta. (2 figures, 1 table, 22 references)—David Shoch

Cone cell-specific genes expressed in retinoblastoma. Bogenmann, E., Lochrie, M. A., and Simon, M. I. (Div. Hematology-Oncology, Children's Hosp. of Los Angeles, Los Angeles, CA 90027). Science 240:76, 1988.

The authors grew retinoblastoma cells in vitro and showed that the cells expressed highly specialized photoreceptor genes. Transcripts for a unit specific to the cone cell were found in seven of seven retinoblastoma cell lines. There were also transcripts for the red and green cone cell photopigments. There were no marker genes specific to rod cells. Therefore, the origin of retinoblastoma is most likely a cone cell. (3 figures, 1 table, 24 references)—David Shoch

NEWS ITEMS

Send News Items to American Journal of Ophthalmology 435 N. Michigan Ave., Suite 1415 Chicago, IL 60611

The Journal invites readers to submit announcements concerning meetings, postgraduate courses, lectures, honors, and appointments. Each item must be typed double-spaced on bond paper with 1½-inch margins. Only one news item should be submitted on each page. Announcements concerning meetings and courses must contain the title, location, dates, sponsors, and address required for additional information. Each item must not exceed 75 words in length. Announcements of meetings and courses must be received at least four months before the event.

International Congress on Ocular Trauma

An International Congress on Ocular Trauma will be held Feb. 19-24, 1989, in Tel-Aviv, Israel. For further information, write The Secretariat, International Congress on Ocular Trauma, P.O.B. 50006, Tel-Aviv 61500, Israel.

Fifth International Retinitis Pigmentosa Congress

The Fifth International Retinitis Pigmentosa Congress will be held Nov. 4–7, 1988, in Melbourne, Australia. For further information, write Leonie Kelleher, 46A Oxley Road, Hawthorn, Victoria 3122, Australia.

Hong Kong Ophthalmological Society: Hong Kong Clinical Ophthalmological Symposium

The Hong Kong Ophthalmological Society will sponsor the Hong Kong Clinical Ophthalmological Symposium, Dec. 2–4, 1988, in Hong Kong. For further information, write Patrick C. P. Ho, M.D., Chairman, c/o Secretariat Office, Exhibition and Convention Division, Room 810-814, Wing On Plaza, 62 Mody Road, Tsimshatsui East, Kowloon, Hong Kong.

Armed Forces Institute of Pathology and American Registry of Pathology: Annual Courses

The Armed Forces Institute of Pathology and the American Registry of Pathology will conduct their Annual Courses: Anatomy, Histology, and Electron Microscopy of the Eye, Orbit and Ocular Adnexa, Aug. 20 and 21, 1988, and Ophthalmic Pathology for Ophthalmologists, Aug. 22–26, 1988. For further information, write Executive Director, American Registry of Pathology, Armed Forces Institute of Pathology, Washington, DC 20306-6000.

American Society of Ophthalmic Plastic and Reconstructive Surgery: Annual Meeting

The Annual Meeting of the American Society of Ophthalmic Plastic and Reconstructive Surgery will be held Oct. 7, 1988, in Las Vegas, Nevada. For further information, write Daniel L. McLachlan, M.D., 122 S. Michigan Ave., Suite 1427, Chicago, IL 60603.

Contact Lens Association of Ophthalmologists: Annual Meeting

The Contact Lens Association of Ophthal-mologists will hold its annual meeting Jan. 18–21, 1989, in New Orleans, Louisiana. For further information, write Meetings Registrar, CLAO, 523 Decatur St., Suite One, New Orleans, LA 70130.

Alabama Academy of Ophthalmology: Annual Scientific Meeting

The Alabama Academy of Ophthalmology will hold its annual scientific meeting July 27–31, 1988, in Destin, Florida. For further information, write Carla J. Meeks, Alabama Academy of Ophthalmology, P. O. Box 11252, Birmingham, AL 35202.

Georgetown University: Office Practice in Ophthalmology Course

Georgetown University will sponsor a course, Office Practice in Ophthalmology, Oct. 21–22, 1988, in White Sulphur Springs, Virginia. For further information, write Office of Continuing Medical Education, Georgetown University Medical Center, 3800 Reservoir Rd., N.W., Washington, D.C. 20007.

Hawaiian Eye Foundation: Tenth Annual Royal Hawaiian Eye Meeting

The Hawaiian Eye Foundation will sponsor the Tenth Annual Royal Hawaiian Eye Meeting, Jan. 14–21, 1989, in Kauai Lagoons, Kauai, Hawaii. For further information, write Hawaiian Eye Foundation, c/o Mary Charles & Associates, 2334 South King Street, Suite 205, Honolulu, HI 96286.

Humana Hospital Lexington: Fourth Annual Multispecialty Oculoplastic Surgery Symposium

The Ophthalmology Center of Excellence at Humana Hospital-Lexington will sponsor the Fourth Annual Multispecialty Oculoplastic Surgery Symposium, Sept. 3–5, 1988, in Lexington, Kentucky. For further information, write Jennifer DePrima Richard, Ophthalmology Center, Humana Hospital-Lexington, 150 N. Eagle Creek Dr., Lexington, KY 40509.

Pennsylvania State University: Annual Neuro-Ophthalmology Conference

Pennsylvania State University will hold the Annual Neuro-Ophthalmology Conference, Aug. 31 and Sept. 1, 1988, in Hershey, Pennsylvania. For further information, write Jane C. Mihelic, Office of Continuing Medical Education, Pennsylvania State University, 501 J. Orvis Keller Building, University Park, PA 16802

Sainte-Justine Hospital: Thirteenth Annual Pediatric Ophthalmology Day

Sainte-Justine Hospital will sponsor the Thirteenth Annual Pediatric Ophthalmology Day, Oct. 21, 1988, in Montreal, Canada. For further information, write Jean Milot, M.D., Department of Ophthalmology, Hospital Sainte-Justine, 3175 Côte Sainte-Catherine, Montreal, P.Q. H3T 1C5 Canada.

West Virginia University: Ninth Annual Ophthalmology Conference

The Department of Ophthalmology of West Virginia University will hold its Ninth Annual Ophthalmology Conference Oct. 14 and 15, 1988, in Morgantown, West Virginia. For further information, write West Virginia University School of Medicine, Department of Ophthalmology, Morgantown, WV 26506.

Personals.

D. Jackson Coleman

D. Jackson Coleman received the Lucien Howe Award of the State University of New York at Buffalo School of Medicine and Biomedical Sciences and the Buffalo Ophthalmological Society on April 21, 1988.

Gunter K. von Noorden

Gunter K. von Noorden presented the Sir William Bowman Lecture, "Current Concepts of Infantile Esotropia," and received the Bowman Medal during the Annual Congress of the Ophthalmological Society of the United Kingdom in Harrogate, England, April 20–22, 1988.

National Advisory Eye Council: New Members

At the meeting of the National Advisory Eye Council Carl Kupfer introduced John T. Flynn and Bruce E. Spivey, new members of the Council.

AMERICAN JOURNAL OF OPHTHALMOLOGY

Monthly since 1884

ORIGINAL ARTICLES

Traumatic Hyphema

Kennedy, Brubaker

Optic Disk Neovascularization in Diabetes

Wilson, Stefánsson, Klombers, Hubbard, Kaufman,

Cryopexy for Peripheral Uveitis

Devenyi, Mieler, Lambrou, Will, Aaberg

Scleral Findings in Uveal Effusion

Ward, Gragoudas, Pon, Albert

Fluid-Gas Exchange for Hypotony

Stallman, Meyers

Pseudoinflammatory Macular Dystrophy

Dreyer, Hidayat

Betaxolol in Glaucoma and Pulmonary

Disease

Weinreb, van Buskirk, Cherniack, Drake

β-Blockers and Postoperative Intraocular

Pressure

West, Lischwe, Thompson, Ide

Intraocular Pressure Assessment in Gas-Filled Eyes

Hines, Jost, Fogelman

Visual Field Indices in Glaucoma

Seamone, LeBlanc, Rubillowicz, Mann, Orr

Tear Analysis in Graves' Ophthalmopathy

Khalil, de Keizer, Kijlstra

Optic Atrophy in Children

Repka, Miller

Benign Orbital Schwannomas

Byrne, van Heuven, Lawton

Visual Field Defects in Ischemic Optic

Neuropathy

Kline

Nasolacrimal Obstruction After Orbital Decompression

Seiff, Shorr

Corneal Edema and Hibiclens

Phinney, Mondino, Hofbauer, Meisler, Langston, Forstot, Benes

Suramin Keratopathy

Holland, Stein, Palestine, LaRocca, Chan, Kuwabara, Myers, Thomas, McAtee, Nussenblatt

Corneal Calcification in Werner's Syndrome

Kremer, Ingber, Ben-Sira

• EDITORIAL

Potential Use of Quinolones in Future Ocular Antimicrobial Therapy

Borrmann, Leopold

• LETTERS TO THE JOURNAL

Polypeptide in aqueous humor

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Optic disk neovascularization

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Treatment of encapsulated blebs

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Good, Stern

Lacrimal anomalies in Brachmann-de Lange's syndrome

Vila-Coro, Arnoult, Robinson, Mazow

Lacrimal abscess caused by Eikenella

Dua, Paterson, Smith, Scott, Forrester

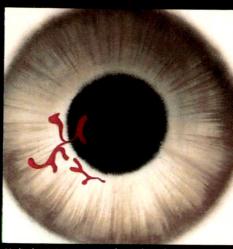


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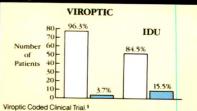
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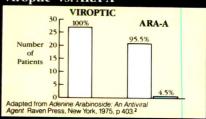


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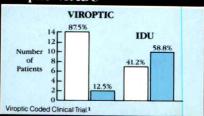
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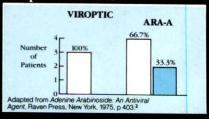
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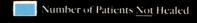
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Traumatic Hyphema in a Defined Population

Robert H. Kennedy, M.D., and Richard F. Brubaker, M.D.

From 1960 through 1984, traumatic hyphema was diagnosed in 248 residents (204 males and 44 females) of Olmsted County, Minnesota. The mean annual incidence rate was significantly greater (P < .001) among males than among females: 20.2 per 100,000 population and 4.1 per 100,000, respectively. The overall mean annual rate was 12.2. A significant increase in the incidence rate in recent years was caused primarily by an increase in the number of sports-related injuries. Secondary hemorrhage occurred in 18 patients (7.3%) and was significantly (P < .05) more frequent among patients whose initial hyphema filled more than one third of the anterior chamber. The low risk of secondary hemorrhage and associated serious sequelae suggests that the possible benefits from routine systemic administration of aminocaproic acid may not outweigh the costs and risks in populations similar to that of Olmsted County.

THE MOST APPROPRIATE therapy for traumatic hyphema is uncertain. Suggested regimens for decreasing the frequency of secondary hemorrhage include strict bed rest, sedation, patching of one or both eyes, use of cycloplegic and

miotic drugs, systemic administration of corticosteroids, and hospitalization. ¹⁻⁸ Several randomized, double-masked clinical trials of aminocaproic acid have found it to be effective in decreasing the frequency of secondary hemorrhage. ⁹⁻¹¹ However, because of perceived weaknesses of the clinical trials, ^{12,13} the cost, the undesirable side effects associated with use of aminocaproic acid, and the relatively low frequency of secondary hemorrhage in certain populations, ^{4,14-17} the question of whether it should be prescribed routinely for all patients with traumatic hyphema remains unanswered.

We conducted this study to collect information regarding the incidence rates of traumatic hyphema and frequency of secondary hemorrhage and to evaluate trends from 1960 through 1984 in the population of Olmsted County, Minnesota. We also assessed trends in the types of injuries that led to traumatic hyphema and examined possible risk factors for secondary hemorrhage.

Material and Methods

In order to calculate incidence rates for a disease or injury, it is necessary to identify virtually all persons in a defined population who newly develop that condition during the period of study. The medical information systems of the Mayo Clinic and the Rochester Epidemiology Project provide a resource for such studies in the population of Olmsted County, Minnesota. 18,19 Surgical procedures and diagnoses recorded by ophthalmologists at the Mayo Clinic and at the other medical facili-

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From the Department of Ophthalmology, Mayo Clinic and Mayo Foundation. This study was supported in part by Research grants EY-02037 and AM-30582 from the National Institutes of Health and by a grant from Research to Prevent Blindness, Inc. Dr Kennedy is a 1988–1989 Heed Foundation Fellow.

ties that serve local residents are entered into this central computer-based system.

We reviewed the original medical records for all county patients identified, through this system, as having had traumatic hyphema not associated with an operation or with penetrating injury of the globe from 1960 through 1984. Hyphema was considered to be present if a layer of blood or clot or if circulating erythrocytes were observed in the anterior chamber.

The demographic and clinical information collected included age, sex, type of injury, visual acuity, extent of hyphema, associated injuries, duration of hospital stay, types of therapy, and all complications. Secondary hemorrhage was considered to be present if a definite increase in the total amount of blood in the anterior chamber was noted at any time after the initial examination. In general, the patients in this study were examined at least twice per day during the early period after the injury.

The denominators used in the calculation of incidence rates were based on federal census data for Olmsted County. Overall incidence rates were adjusted by age and sex and the sex-specific rates by age to the 1970 white population of the United States. The significance of differences in incidence rates were assessed using confidence intervals calculated from tables of the cumulative Poisson distribution. The χ^2 method and Fisher's exact test were

applied to test for significant differences between subgroups of patients with regard to various characteristics. Wilcoxon rank-sum procedures were used for comparisons that involved continuous variables. The probability of secondary hemorrhage was evaluated multivariately with a stepwise logistic regression model.

Results

From 1960 through 1984, traumatic hyphema was diagnosed in 248 patients (204 males and 44 females). The ages at diagnosis ranged from 0 (trauma at birth) to 87 years (median, 15.5 years). The mean annual incidence rates per 100,000 population were 20.2 for males, 4.1 for females, and 12.2 for the total group. The difference in incidence rate between males and females was statistically significant (P < .001). For both sexes, the incidence rates peaked at ages 10 to 19 years (Fig. 1). The distribution of patients by year of diagnosis is shown in Figure 2. Growth in the number of patients seen annually was a result mainly of an increase in the incidence rates of traumatic hyphema rather than changes in size of the population. The mean annual incidence rate was 15.9 per 100,000 population for the period 1973 through 1984 and 7.9 for 1960 through 1972 (P < .001).

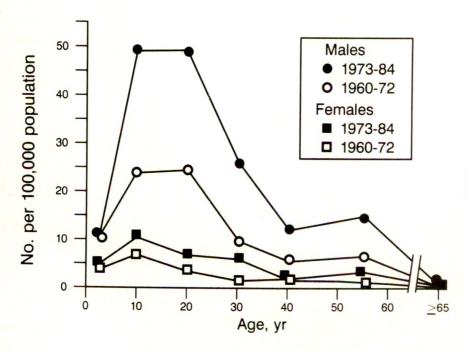


Fig. 1 (Kennedy and Brubaker). Mean annual incidence rates of traumatic hyphema by age and sex for the periods 1960 through 1972 and 1973 through 1984.

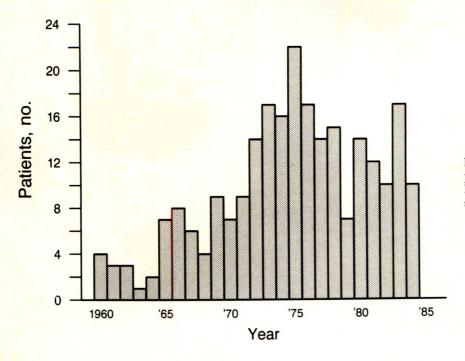


Fig. 2 (Kennedy and Brubaker). Distribution of patients with traumatic hyphema by year of diagnosis, 1960 through 1984.

Much of this increase occurred among young males (Fig. 1).

Projectiles accounted for nearly two thirds of the injuries; most of the remaining injuries were associated with blows from various objects (Table 1). Analysis of trends over time showed a striking increase in the number of injuries that were related to participation in sports activities (Table 2). The proportion of such injuries for the period 1973 through 1984 (74 of 171, 43.3%) was significantly greater (P < .01) than that for preceding years (18 of 77, 23.4%). Most of this increase was associated with softball, racquetball, and hockey.

Ophthalmic abnormalities associated with traumatic hyphema were found in nearly all parts of the globe as well as in surrounding structures (Table 3). The most common findings included corneal abrasion, recession of the anterior chamber angle, and retinal edema. Secondary hemorrhage occurred in 18 patients (7.3%), all of whom were examined during the first five days after injury (median, three days).

The initial hyphema was less than one third of the volume of the anterior chamber in 222 patients (89.5%) (Table 4). The frequency of secondary hemorrhage among those patients was significantly less (P < .05) than among patients with larger hyphemas. Of the 23 patients with initial hyphemas that filled one third or more of the anterior chamber, five (21.7%) had secondary hemorrhage. There

were no statistically significant differences between those who did and those who did not have secondary hemorrhage with regard to age, sex, cause of injury (projectile, blow, or explosion), or time from injury to initial examination. This time interval was one day or less for 236 (95.2%) of the 248 patients.

A stepwise logistic regression model was fitted for secondary hemorrhage vs age, sex, days from injury to initial examination, cause of injury, and initial extent of hyphema. Initial extent of hyphema (P < .01) and days from injury to initial examination (P < .05) were both related positively to the occurrence of secondary hemorrhage. Age, sex, and cause of injury did not contribute significantly to the fit of the model.

Most of the patients were admitted to the hospital and treated by patching of one or both eyes, bed rest, and cycloplegic medications (Table 5). There were no statistically significant differences in the use of these measures or of corticosteroids applied topically between patients who had secondary hemorrhage and those who did not. None of the five patients who received aminocaproic acid had a secondary hemorrhage later. One additional patient who was given aminocaproic acid after secondary hemorrhage had already occurred recovered without any further bleeding. Systemic corticosteroid therapy was not prescribed for any of the patients.

TABLE 1

CAUSES OF TRAUMATIC HYPHEMA IN OLMSTED COUNTY, MINNESOTA, 1960 THROUGH 1984

	PATIENTS				
CAUSE	NO.	%			
Projectile	164		66.1		
Ball	61	24.6			
Dirt or stone	14	5.6			
Slingshot pellet	12	4.8			
BB	11	4.4			
Food or nut	8	3.2			
Snowball	6	2.4			
Lawn mower	6	2.4			
Hammering	5	2.0			
Hockey puck	5	2.0			
Wood chip	5	2.0			
Other	31	12.5			
Blow	75		30.2		
Stick	25	10.1			
Fist, finger, or elbow	16	6.5			
Flexible object (rope,					
hose, etc.)	11	4.4			
Fall	10	4.0			
Other	13	5.2			
Explosion	6		2.4		
Battery	2	0.8			
Pressure pump	1	0.4			
Tire	1	0.4			
Fuse	1	0.4			
Roll of caps	1	0.4			
Unknown	3		1.2		
Total	248		100.0		

Of the 18 patients who had secondary hemorrhage, visual acuity returned to 20/20 or better in 14 (77.8%). Visual acuities of 20/25, 20/30, and 20/50 were recorded for three of the other patients. The final patient, who had total hyphema initially, had a marked increase in intraocular pressure when secondary hemorrhage occurred and the anterior chamber again filled completely. Even though paracentesis of the anterior chamber was performed twice, blood staining of the cornea developed and visual acuity remained at light perception. Several years later, visual acuity was recorded as no light perception, marked scarring of the

TABLE 2

TYPES OF SPORTS ACTIVITIES ASSOCIATED WITH TRAUMATIC HYPHEMA, BY DATE OF DIAGNOSIS IN OLMSTED COUNTY, MINNESOTA, 1960 THROUGH 1984

	NO. OF PATIENTS							
SPORT	1960– 1964	1965– 1969	1970– 1974	1975– 1979	1980– 1984	TOTAL		
Softball	0	3	5	6	10	24		
Racquetball	0	0	2	8	8	18		
Hockey	0	1	6	8	2	17		
Tennis	1	1	5	2	2	11		
Basketball	0	0	1	3	0	4		
Other	0	2	6	4	6	18		
Total	1	7	25	31	28	92		

cornea was present, and the patient requested enucleation.

Four of the 17 other patients had marked increase of intraocular pressure at the time of secondary hemorrhage and underwent paracentesis of the anterior chamber. Hospitalization for all 18 patients who had secondary hemorrhage ranged from three to 21 days (median, 6.5 days). For the 13 patients who were admitted to the hospital at the time of diagnosis of the initial hyphema, the median duration of hospital stay was eight days, significantly greater (P < .01) than the median, five days, among the 181 patients who were admitted to the hospital but who did not have secondary hemorrhage.

Discussion

We are aware of only one previous estimate of the incidence rate of traumatic hyphema. Agapitos, Noel, and Clarke¹⁷ found the mean annual incidence rate to be 17 per 100,000 population less than 18 years of age in a predominantly white community in Canada. This is similar to the mean annual age- and sexadjusted (to the 1970 white population of the United States) rate, 20.7 per 100,000 population less than 20 years of age in Olmsted County.

Because some patients in Olmsted County probably did not seek medical care after an ocular injury, the incidence rates reported here may be too low. However, although it is difficult to quantify underascertainment of patients, all indications are that it was small. An adequate number of ophthalmologists to pro-

TABLE 3
OPHTHALMIC FINDINGS ASSOCIATED WITH
TRAUMATIC HYPHEMA IN OLMSTED COUNTY,
MINNESOTA, 1960 THROUGH 1984

		PATIENTS*		
SITE	FINDING	NO.	%	
Orbit Eyelid or	Fracture	3	1.2	
eyebrow	Laceration	41	16.5	
Globe	Secondary hemorrhage Increased intraocular	18	7.3	
	pressure (>25 mm Hg)	9	3.6	
Cornea	Abrasion	100	40.3	
	Laceration	7	2.8	
	Blood staining	1	0.4	
Angle by	Recession	26	28.6	
gonioscopy [†]	Peripheral anterior			
	synechiae.	3	3.3	
	Normal	62	68.1	
Iris	Traumatic mydriasis	18	7.3	
	Dialysis	6	2.4	
	Posterior synechiae	1	0.4	
Lens	Cataract	13	5.2	
	Subluxation of lens	3	1.2	
Vitreous	Hemorrhage	21	8.5	
Retina	Macular edema	26	10.5	
	Peripheral edema	22	8.9	
	Hemorrhage	23	9.3	
	Macular scar	6	2.4	
	Detachment	3	1.2	
	Dialysis	1	0.4	
Choroid	Rupture	5	2.0	
Optic nerve	Injury	1	0.4	

^{*}Several patients had more than one finding. Percentages are based on 248 patients.

vide care for local patients was available throughout the period of the study, and few socioeconomic barriers exist in the population studied to hinder patients from seeking medical care. Additionally, of the 248 patients, 236 (95.2%) were seen within one day after injury and only one patient was initially examined at some time after injury because of a presumed secondary hemorrhage. Any patients who did not seek medical care probably would have had a less severe spectrum of injuries than those who did. To the extent that this occurred, it would have had the effect of spuriously in-

TABLE 4

EXTENT OF HYPHEMA AT DIAGNOSIS AMONG PATIENTS WITH AND WITHOUT SECONDARY HEMORRHAGE IN OLMSTED COUNTY, MINNESOTA, 1960 THROUGH 1984

	SEC	ONDARY	HEMOF	RHAGE		
EXTENT OF		YES = 18)	NO (N = 230)		% WITH SECONDARY	
HYPHEMA*	NO.	%	NO.	%	HEMORRHAGE	
Microscopic	5	27.8	74	32.2	6.3	
> Microscopic, < 1/3	8	44.5	135	58.7	5.6	
≥ 1/3, < 1/2	3	16.7	14	6.1	17.6	
≥ 1/2, < total	1	5.5	3	1.3	25.0	
Total	1	5.5	1	0.4	50.0	
Unknown	0	0.0	3	1.3	0.0	
Overall	18	100.0	230	100.0	7.3	

^{*}Proportion of anterior chamber filled with blood.

creasing the observed frequencies of secondary hemorrhage and other associated ophthalmic findings in the study group. Therefore, the relatively low rate of complications also seems to indicate that the level of case ascertainment was high.

In agreement with information from series of cases, 3,4,6,16,20-23 the age- and sex-specific incidence rates of traumatic hyphema were highest among children and young adults, and males were at greater risk than females. Between the first 13 years of the study and the more recent years, there was an increase in the proportion of microscopic hyphemas, from 24.7% (19 of 77 patients) to 35.1% (60 of 171 patients), but this trend was not statistically significant. Therefore, the twofold increase in incidence rates was, in all likelihood, mainly the result of increased occurrence of traumatic hyphema rather than improved recognition and diagnosis of less severe injuries.

The distribution of injuries by cause in the population of Olmsted County was similar to distributions in large metropolitan areas. 8,16,24-28 Approximately two thirds of the injuries were associated with trauma from projectiles; most of the rest were from blows from various objects. Nearly half of all injuries in the most recent five-year period were sports related, and much of the overall increase in incidence rates in recent years was because of an increase in the number of sports-related injuries. These data document the importance of participation in sports activities, particularly those that re-

¹The percentages for this group are based on the 91 patients who had gonioscopic examination.

FREQUENCY OF SECONDARY HEMORRHAGE IN 248
PATIENTS ACCORDING TO TREATMENT REGIMENS
FOR TRAUMATIC HYPHEMA IN OLMSTED COUNTY,
MINNESOTA, 1960 THROUGH 1984

	TOTAL NO. OF	SECONDARY HEMORRHAGE		
TREATMENT	PATIENTS	NO.	%	
Patching of eye				
Unilateral	64	3	4.7	
Bilateral	134	12	9.0	
None	26	1	3.8	
Unknown	24	2	8.3	
Topical cycloplegics				
Yes	124	2	8.9	
No	122	7	5.7	
Unknown	2	0	0.0	
Topical corticosteroid	ds			
Yes	45	3*	6.7	
No	203	15	7.4	
Bed rest				
Yes	221	17	7.7	
No	26	1	3.8	
Unknown	1	0	0.0	
Admission to hospita	ı			
Yes	194	13	6.7	
No	54	5	9.3	

^{*}Four additional patients were treated with topical corticosteroids after secondary hemorrhage occurred.

quire close proximity to small objects traveling at relatively high velocity, as a leading cause of traumatic hyphema. This suggests that further efforts to educate participants and increase the use of protective eyewear might decrease the incidence rates of traumatic hyphema. Although we have no specific data regarding use of protective eyewear by hockey players in Olmsted County, the decrease in injuries associated with hockey observed in recent years might be the result of such a preventive measure.

Several variables influence the value of any measure suggested for the prevention of secondary hemorrhage. Among the most important are the frequency of secondary hemorrhage and the frequency and severity of the associated complications. Other factors include whether use of the preventive measure would be practical, economically feasible, and acceptable to patients and whether the frequency of side

effects or complications would be acceptably low. The reported frequencies of secondary hemorrhage show considerable variability, ranging from approximately 2% to 38%. 3-11,14-17,20-42 To what extent this reflects differences in diagnostic criteria and study methods as opposed to true differences in risk remains unknown.

Selective referral of certain patients once a complication has occurred or of those patients with more severe injuries may influence the observed incidence of secondary hemorrhage among patients seen at academic centers. In the study with the highest reported frequency of secondary hemorrhage (38%), it was noted that several patients had been referred (and consequently included in the study) only after secondary hemorrhage had already occurred. Some of the variability in reported frequencies also might be because of population differences in regard to the proportion of patients with various levels of severity of traumatic hyphema who seek medical care.

Some investigators have reported the rates of secondary hemorrhage separately by race. 9,20,29,34,40,42 In two of those studies, blacks experienced secondary hemorrhage significantly more often than whites or than whites and Hispanics combined (P < .05). ^{29,34} The other studies showed no statistically significant racial differences. The presence of sickle cell hemoglobin could not have accounted for the difference observed by Palmer and associates²⁹ because patients with sickle cell hemoglobin were not included in the study. Skalka³⁴ noted that sickle cell trait was documented in only one patient in his series. In discussing other factors that could have accounted for the racial difference, he indicated that blacks with small hyphemas probably were less likely than whites to be seen at the hospital. Additionally, a larger number of BB injuries occurred among blacks. In general, the lowest rates of secondary hemorrhage (10% or less) have been observed in Northern European populations 14,30,31,38 and in other white populations in Canada, 15,17,37 Australia, 35,36 and the United States,4 including Olmsted County.

The severity of injury, as indicated by the amount of blood in the anterior chamber at diagnosis, has been suggested to correlate with outcome as measured by frequency of complications and final visual acuity. ^{3-6,17,20,22,26-28,33} According to our calculations, at least six studies have demonstrated significantly higher rates (P < .05) of secondary hemorrhage among

patients with larger initial hyphemas. 4,6,17,26,27,33 Other reports also suggest such a trend but the results are not statistically significant. 3,16,35 We are not aware of any data that show a significant trend in the opposite direction. In the present study, the risk of secondary hemorrhage was significantly greater (P < .05) among patients with initial hyphemas filling more than one third of the anterior chamber.

Further information regarding risk factors might explain some of the variability in reported frequencies of secondary hemorrhage. It is especially needed for planning future clinical trials of measures to prevent secondary hemorrhage and for developing guidelines for the use of these measures. For example, treatment with aminocaproic acid has been demonstrated to lessen the frequency of secondary hemorrhage in several randomized double-masked clinical trials.9-11 ophthalmolo-However, many gists4,12,13,15 remain unconvinced of its value for routine use in most patients with traumatic hyphema, primarily because of undesirable side effects (nausea, vomiting, and hypotension), cost, and perceived weaknesses of the clinical trials. Clearly, the cost/benefit and risk/ benefit ratios may be quite different in populations or subgroups of patients with only a 5% risk of secondary hemorrhage relative to those in populations (such as patients with initial hyphemas that fill more than one third of the anterior chamber) with a 20% or higher risk. Allingham and associates43 have been working to formulate aminocaproic acid for topical ocular use. This therapeutic approach might diminish the frequency and severity of systemic side effects as well as the cost of treatment, making use of aminocaproic acid more reasonable in populations with low rates of secondary hemorrhage.

Another measure suggested for management of patients with traumatic hyphema that should be examined carefully is hospitalization. Routine admission of patients with traumatic hyphema is costly and seems to have little effect on the risk of secondary hemorrhage. Admission may be useful, however, to allow close observation and to ensure compliance with treatment regimens for selected patients at high risk for complications.

Our findings suggest that one of the best means for lessening the morbidity associated with traumatic hyphema would be to improve primary prevention of ocular injuries through increased use of protective eyewear during participation in sporting events.

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Optic Disk Neovascularization and Retinal Vessel Diameter in Diabetic Retinopathy

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We measured retinal vessel diameter before and after panretinal photocoagulation in 59 eyes with diabetic retinopathy and moderate to severe optic disk neovascularization. Treatment significantly reduced mean arteriolar and venular diameter. The diameter of the retinal arterioles after treatment correlated significantly with the amount of regression in disk neovascularization. Eyes with large diameter vessels after treatment usually had little or no regression of proliferative retinopathy, whereas regression was more frequently seen in eyes with smaller diameter vessels after treatment.

Previous Studies have shown that retinal vessel diameter, blood velocity, and pulsatility decrease after panretinal photocoagulation. 1-4 The relationship of these vascular changes to the regression of proliferative diabetic retinopathy is uncertain. We believe that thin, atrophic retinal vessels are associated with involuted or inactive neovascular disease and dilated vessels with persistent or progressive disease.

We studied retinal vessel diameter and disk neovascularization in color fundus photographs obtained from the Diabetic Retinopathy Study.⁵⁻⁹ The Diabetic Retinopathy Study research group proved that disk neovascularization was an important risk factor for the development of severe visual loss. We sought to determine how the diameter of the retinal vessels and the regression of optic disk neovascularization were related.

Material and Methods

We studied color fundus photographs of 59 eyes that had undergone argon laser panretinal photocoagulation at three Diabetic Retinopathy Study clinics. All photographs were 30-degree fields, centered on the optic disk. The eyes were selected at random from among those meeting the following criteria: absence of vitreous hemorrhage on the pretreatment photograph, at least three high risk factors for severe visual loss, and moderate to severe disk neovascularization. Visual acuity data were obtained from the Diabetic Retinopathy Study files for all eyes studied.

We measured retinal vessels on the baseline and four-month posttreatment photographs. Superotemporal, superonasal, inferotemporal, and inferonasal vessels were measured within 1 disk diameter of the disk margin. Measurements were not attempted when localized hemorrhage prevented good visualization.

Photographs were projected onto a flat white screen and the projection apparatus was adjusted to conceal photocoagulated areas as much as possible. Vessel diameters were then measured by a masked investigator and, for convenience, expressed in micrometers by using the horizontal diameter of the optic disk (1,500 µm) as a size reference. Individual variation in disk diameter did not significantly influence the study results, since they could be reproduced using the raw vessel diameter measurements.

Two independent graders measured disk neovascularization at the Diabetic Retinopathy Study reading center during the course of the

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clinical study. A five-unit scale was used: 0, no neovascularization; 1, questionable neovascularization; 2, definite neovascularization, but less than in standard photograph 10A; 3, neovascularization equal to or worse than in photograph 10A, but less than in standard photograph 10C; and 4, neovascularization equal to or worse than in photograph 10C. 9 In the present study, grades 3 and 4 represented moderate and severe disk neovascularization, respectively.

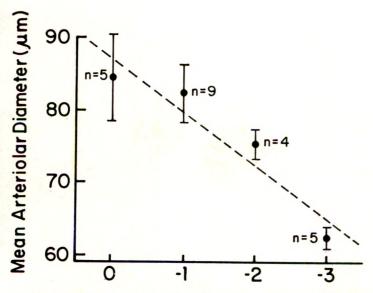
Results

Mean vessel diameter (average of all quadrants) decreased after photocoagulation: arterioles decreased by $9.7\% \pm 2.0\%$ (mean ± 1 S.E.M.; n = 23; P < .001, t-test) and venules decreased by $8.0\% \pm 1.8\%$ (n = 21; P < .001). No significant regional differences were noted. Eyes that showed no change (or an increase) in disk neovascularization grade four months after treatment generally demonstrated smaller reductions in vessel diameter, averaging $5.1\% \pm 1.4\%$ (n = 5) in arterioles and $4.7\% \pm 2.6\%$ (n = 7) in venules. These reductions were not statistically different from zero reduction among the arterioles in each quadrant and overall among venules.

A significant correlation was found between

posttreatment arteriolar diameter and regression in disk neovascularization (posttreatment minus pretreatment grade) (Figure). Pretreatment arteriolar diameter did not show a similar correlation. After photocoagulation, relatively small vessel diameters were consistently noted in eyes with regression of three or more grades in disk neovascularization (Table), and occasionally noted in eyes with lesser degrees of regression. Relatively large vessel diameters were generally found in eyes that showed little or no neovascular regression (zero or one grade).

An analysis of the visual acuity data showed that disk neovascularization was an important risk factor for the development of severe visual loss in our sample (visual acuity worse than 5/200 on two consecutive four-month follow-up visits), as was found in the Diabetic Retinopathy Study. Severe visual loss occurred in ten of 17 eyes (59%) with unchanged or increased disk neovascularization after photocoagulation, and ten of 42 eyes (24%) that had decreased neovascularization. The primary determinant of the occurrence of severe visual loss appeared to be the grade of disk neovascularization after treatment (chi-square = 11.57; P = .02). Eyes that developed severe visual loss had, on average, larger posttreatment arteriolar and venular diameters than those that did not develop severe visual loss, but this difference was not satistically significant.



Change in Disc Neovascularization (grades)

Figure (Wilson and associates). Posttreatment vessel diameter in micrometers (mean of four arterioles) vs change in neovascularization grade (pretreatment minus posttreatment). Dashed line represents the calculated linear regression (r = .62, P = .002).

TABLE					
VESSEL DIAMETER AFTER PHOTOCOAGULATION AND REGRESSION IN DISK NEOVASCULARIZATION					

	RED			
VESSEL MEASURED	NONE (0 GRADES)	LOW (1 OR 2 GRADES)	HIGH (3 OR 4 GRADES)	P VALUE [†]
Arterioles				
Superotemporal	$86 \pm 5 (9)$	$85 \pm 3 (20)$	78 ± 3 (9)	NS
Inferotemporal	83 ± 4 (9)	$82 \pm 4 (21)$	$69 \pm 5 (8)$	NS
Superonasal	77 ± 8 (7)	76 ± 3 (18)	$61 \pm 6 (7)$.049
Inferonasal	$73 \pm 4 (8)$	$68 \pm 4 (16)$	56 ± 3 (7)	.009
All arterioles (mean)	85 ± 6 (5)	80 ± 3 (13)	64 ± 2 (5)	.002
Venules				
Superotemporal	$139 \pm 9 (12)$	$123 \pm 5 (22)$	104 ± 6 (8)	.006
Inferotemporal	$131 \pm 7 (9)$	$121 \pm 5 (24)$	112 ± 4 (11)	.028
Superonasal	$103 \pm 8 (9)$	98 ± 7 (18)	$96 \pm 11 (5)$	NS
Inferonasal	92 ± 5 (10)	92 ± 7 (21)	87 ± 8 (5)	NS
All venules (mean)	$114 \pm 2 (7)$	$109 \pm 6 (13)$	$101 \pm 7 (2)$	NS

^{*}Mean ± 1 S.E.M. vessel diameter (μm); number of eyes in parentheses.

Discussion

We found that retinal vessel diameter after panretinal photocoagulation was related to the degree of regression in disk neovascularization. This correlation has not been previously studied in detail, and our findings support our hypothesis that inactive or regressed proliferative retinopathy is generally associated with attenuated retinal branch vessels.

Comparatively small vessel diameter was usually found in eyes showing a large regression in neovascularization, but was occasionally noted in association with lesser degrees of regression. Relatively dilated retinal vessels following treatment were, however, more indicative of disk neovascularization status, since these vessels were generally found in eyes that showed little or no neovascular regression.

Vessel diameters in eyes that developed severe visual loss were, on average, slightly larger than in eyes that did not develop severe visual loss. However, since this difference was not significant, and since we attempted to select a homogeneous risk group at the outset, no conclusion can be drawn as to whether vessel diameter may relate to visual outcome. Additionally, the application of retreatment photocoagulation throughout the five-year course of

the Diabetic Retinopathy Study complicates the predictive value of early fundus photographs.

While the efficacy of photocoagulation for proliferative diabetic retinopathy is well established, its mechanism of action remains uncertain. Clinically, a reduction in vessel diameter is usually apparent several weeks after treatment, but its relationship to the regression of retinopathy is unknown. In animal studies, oxygen has been implicated as a mediator of vasoconstriction following panretinal photocoagulation. Such experiments have shown an increased pO2 concentration adjacent to areas of photocoagulated retina. 11-15 Destruction of the mitochondrion-rich photoreceptor cell layer potentially increases diffusion of choroidal oxygen to the inner retina and may account for the larger observed preretinal oxygen concentrations. Thus, vasoconstriction may be considered an autoregulatory response similar to that observed16 in response to increased concentrations of inspired oxygen. Perhaps the retinal vessels in eyes with the greatest regression in disk neovascularization after panretinal photocoagulation are also more responsive to increased oxygen availability.

Retinal vasoconstriction and associated hemodynamic changes have previously been documented following panretinal photocoagulation. 1-4 Our study suggests that these are

Linear regression; NS, not significant.

not all or nothing physiologic phenomena, but rather graded responses relating directly to the pathophysiology of proliferative diabetic retinopathy.

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Cryopexy of the Vitreous Base in the Management of Peripheral Uveitis

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We reviewed 27 consecutive eyes with peripheral uveitis and vitreous base neovascularization that had been treated with cryopexy and followed up for a median of 4.5 years. During the follow-up period, 21 eyes (78%) remained quiescent, whereas five eyes (18%) demonstrated intermittent inflammation, although only one of these eyes progressed to a traction retinal detachment. One eye (4%) eventually atrophied; however, this was believed to be a result of the ongoing uveitis rather than the cryopexy. The treated eyes had an average improvement of three lines in Snellen visual acuity. We found that corticosteroid therapy remains the primary treatment modality for active inflammation, and vitreous base cryopexy should be reserved for those cases which are resistant to corticosteroids, and which demonstrate active neovascularization.

Peripheral uveitis (pars planitis, intermediate uveitis, peripheral uveoretinitis, and chronic cyclitis) was first described by Schepens in 1947. Since that time, there have been limited advances in the understanding or treatment of this disease.

The disease is characterized by inflammation of the peripheral retina and pars plana, ²⁻⁵ with vitreous base exudation and organization overlying the pars plana. Inflammation invariably begins in the lower half of the eye in the region of the vitreous base, and is usually bilateral. ⁶ As the process progresses, the inflammatory

accumulation spreads superiorly in a circumferential pattern.⁷ The condition becomes symptomatic, with rare exception, in the first three decades of life in otherwise healthy individuals. Histopathologically, the peripheral exudates represent a loose fibrovascular layer containing occasional fibrocyte-like cells and scattered mononuclear cells adjacent to the hyperplastic nonpigmented epithelium of the pars plana.⁸ The course of the disease is variable, ranging from a self-limiting process to one with recurrent exacerbations and remissions.⁹

Various forms of therapy have been used. Some patients require no specific therapy other than observation. Others with more severe disease respond to either topical, retroseptal, or systemic corticosteroids. In 1973, Aaberg, Cesarz, and Flickinger reported success with the use of cryopexy in patients with severe chronic peripheral uveitis recalcitrant to corticosteroid therapy.

In recent years, it has been our clinical impression that eyes with peripheral neovascularization derive particular benefit from cryopexy. The rationale for therapy is to ablate the new vessels, rather than to treat areas of exudation.

We undertook this retrospective study to examine, in particular, those eyes with peripheral uveitis resistant to conventional corticosteroid therapy that have vitreous base neovascularization (type 3 using Aaberg, Cesarz, and Flickinger's classification¹¹) and that were treated with cryopexy.

May 23, 1988. Patients and Methods

From 1977 to 1985, 27 eyes of 18 patients with peripheral uveitis were treated with cryopexy of the vitreous base. All treated eyes demonstrated resistance to corticosteroid therapy (topical, retroseptal, and oral), and all had

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vitreous base neovascularization. Eleven patients (61%) were male and seven (39%) were female. They ranged in age from 6 to 34 years (median, 18 years). The patients were followed up for a median of 4.5 years (range, two to 12 years).

At the initial visit, all patients had a complete ocular examination, including indirect ophthalmoscopy and slit-lamp biomicroscopy. Patients were treated and followed up regularly at the Medical College of Wisconsin until active disease was controlled. At this point, the patients were returned to the care of their referring ophthalmologists. Follow-up information on some patients was attained via a telephone conversation with the referring ophthalmologist.

When applying cryopexy to areas of active neovascularization, either retrobulbar injection of xylocaine or general anesthesia was given, depending primarily on the patient's age. Cryopexy was administered over the involved area of the vitreous base using indirect ophthalmoscopy as described previously.11 It consisted of a freeze, thaw, refreeze technique. A conjunctival incision was not necessary in most cases. All areas of neovascularization were treated, as well as adjacent areas containing dense exudate that were presumed to contain

underlying neovascularization. Uninvolved ciliary body and retina were treated one probe width beyond the recognizable neovasculariza-

Results

A total of 27 eyes in 18 patients were treated. Twenty-three eyes (85%) required only one treatment, three eyes (11%) required two treatments, and one eye (4%) required three treatments before regression of active neovascularization was achieved. Topical corticosteroid therapy was required for varying intervals of time after cryopexy, although generally less than three months.

At the most recent follow-up visit, 21 of the treated eyes (78%) were quiet (defined as demonstrating no cellular reaction in the anterior chamber or vitreous cavity and no active exudation or neovascularization); five eyes (18%) showed mild persistent inflammation (defined as 1+ to 2+ cells in the anterior chamber or vitreous cavity); and one eye (4%) eventually atrophied. In this latter case, the eye had persistent inflammation and developed a traction retinal detachment, necessitating a pars plana

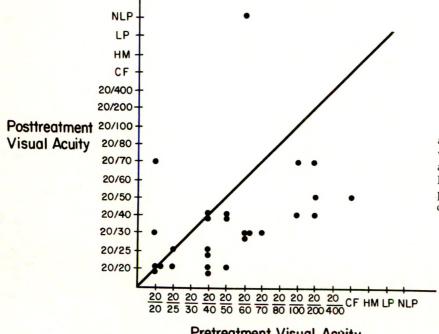


Figure (Devenyi and associates). Visual acuity precryopexy vs final posttreatment visual acuity. CF, counting fingers; HM, hand motions; LP, light perception; NLP, no light perception.

Pretreatment Visual Acuity

vitrectomy with membrane stripping four months after cryopexy. The patient was subsequently followed up for nine years with persistent inflammation, which responded to intermittent periocular and systemic corticosteroid therapy. The eye eventually atrophied and the patient was fitted with a scleral shell.

Eighteen of the 27 treated eyes (67%) demonstrated an improvement in visual acuity (Figure). There was an average of three lines of improvement in Snellen visual acuity between the time of cryopexy and the last follow-up

visit.

Six eyes (22%) showed no change in visual acuity and three eyes (11%), including the eye that atrophied, demonstrated a decrease in visual acuity (Figure). Visual acuity in one eye decreased from 20/20 to 20/70 as a result of macular pucker (for which the patient declined surgical intervention), and visual acuity in another eye decreased from 20/20 to 20/30 because of mild persistent cystoid macular edema and a mild posterior subcapsular cataract. The role of cryopexy vs progression of the underlying disease process in leading to visual loss in these three eyes is not known.

Nine eyes (33%) had persistent cystoid macular edema at the last follow-up visit, five eyes (18%) showed mild epiretinal membrane formation, and six eyes (22%) had varying degrees of posterior subcapsular cataracts. One eye (4%) had both cystoid macular edema and a posterior subcapsular cataract. None of these epiretinal membranes or cataracts were considered significant enough to warrant surgery.

Four of the treated eyes that demonstrated persistent inflammation despite cryopexy eventually required pars plana vitrectomy; these eyes were previously described by Mieler and associates. ¹² The indications for vitrectomy were persistent vitreous inflammation and dense posterior subcapsular cataract (one eye), combined traction/rhegmatogenous retinal detachment (one eye), dense vitreous organization and epiretinal membrane formation (one eye), and persistent vitreous hemorrhage following cryopexy (one eye).

Discussion

Peripheral uveitis is a disease characterized by periodic exacerbations and remissions. Because repeat inflammatory activity often precedes symptoms, patients should be examined at least every three to four months during quiescent periods. ¹³ The disease rarely becomes truly quiescent, however. Peripheral neovascularization correlates with intractable disease and corticosteroid resistance, ⁷ and it is this group of patients whom we believe benefit from vitreous base cryopexy.

In 1973, Aaberg, Cesarz, and Flickinger¹¹ reported success with this form of treatment in a group of 23 eyes. In 35% of the treated eyes, the disease process became inactive, and an additional 57% of eyes showed a marked decrease in activity, requiring no corticosteroid therapy. The treatment group consisted of eyes with severe inflammatory exudation that was resistant to systemic or peribulbar corticosteroid administration. Only 61% of these eyes had definite neovascularization before treatment. This present study included only those patients with definite neovascularization of the vitreous base.

The exact mechanism of action of cryopexy remains unknown. Cryopexy clearly does not treat the underlying cause of pars planitis. We believe the rationale for such ablative treatment is to eliminate the neovascular and ischemic tissue. The elimination of this tissue may result in a decrease in exudate accumulation. Controlling this exudative reaction may decrease the process of organization, possibly resulting in a decreased incidence of traction or traction rhegmatogenous retinal detachments. The activity of the disease can be diminished or arrested in most cases, although the process may progress in some eyes despite therapy.

Peripheral uveitis is a progressive, recurrent disease, with exacerbations and remissions. Careful, long-term follow-up of these eye is essential. Corticosteroid therapy, including topical, periocular, and systemic, remains the primary treatment modality for active inflammation. In those eyes demonstrating inflammation and vitreous base neovascularization, we found that 78% treated with cryopexy became quiescent and remained stable without evidence of further disease progression.

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OPHTHALMIC MINIATURE

Her maiden eyes divine, Fix'd on the floor, saw many a sweeping train Pass by—she heeded not at all: in vain Came many a tiptoe, amorous cavalier, And back retir'd, not cool'd by high disdain; But she saw not: her heart was otherwhere: She sigh'd for Agnes' dreams, the sweetest of the year.

John Keats, "The Eve of St. Agnes," 1820

Abnormal Scleral Findings in Uveal Effusion Syndrome

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We successfully treated a patient with uveal effusion syndrome and abnormal sclera with a partial-thickness sclerectomy. Part of the sclera was immediately cultured, and the excised sclera and the cultured cells were examined by electron microscopy. The sclera demonstrated increased glycosaminoglycan-like deposits between the scleral fibers. The cultured scleral cells showed large intracellular glycogen-like deposits, which were not seen in cells cultured from two control scleras. These findings may be the result of a metabolic defect, which causes a thick, impermeable sclera in some cases of uveal effusion.

CILIOCHOROIDAL EFFUSION or choroidal detachment is the accumulation of fluid in the suprachoroid. Trauma, surgery, inflammatory conditions, arteriovenous fistula, myxedema, tumors, and rhegmatogenous retinal detachment have been implicated as causes of ciliochoroidal effusion. 1,2

Uveal effusion syndrome and nanophthalmos are two other disorders that are frequently linked to ciliochoroidal effusion. The uveal effusion syndrome occurs more frequently in males and is characterized by dilation of episcleral blood vessels, thickened or detached choroid and ciliary body, nonrhegmatogenous retinal detachment with shifting subretinal fluid, a waxing and waning clinical course, and normal intraocular pressure.³

Nanophthalmos is a disorder characterized by a small eye and is usually not associated with systemic disorders or other developmental defects. 4,5 Findings in nanophthalmos include a shallow anterior chamber, narrow angle, high lens/eye volume ratio, and severe hyperopia. 4,6 Serious complications and blindness have been documented after intraocular surgery. 4,6,7 In both uveal effusion syndrome and nanophthalmos, scleral thickening, choroidal effusion, nonrhegmatogenous retinal detachment, and elevated cerebrospinal fluid prohave been reported. levels pathogenesis of ciliochoroidal effusion in these entities remains unknown. We derived some new findings from the sclera of a patient with uveal effusion syndrome that may be related to the pathophysiology of this syndrome.

Case Report

In June 1978, this 57-year-old woman consulted an ophthalmologist for "flashes of light," but no retinal disease was found. In April 1979, reexamination showed a 360-degree elevation of the peripheral retina, with a narrow angle in the right eye. A diagnosis of ring melanoma was considered, and the patient was referred to one of us (E.S.G.) for further diagnosis and treatment.

In May 1979, best-corrected visual acuity was 20/20 with +6.50 diopter sph in each eye. Intraocular pressure was R.E.: 21 mm Hg and L.E.: 16 mm Hg. Slit-lamp biomicroscopy demonstrated mild conjunctival and episcleral injection of the right eye, bilateral shallow anterior chambers, convex irides, and a narrow angle with temporal iridocorneal touch in the right eye. Mild bilateral nuclear sclerosis was noted. No inflammatory cells were seen in the vitreous. Ophthalmoscopy of the right eye showed retinochoroidal folds in the posterior pole (Fig. 1), accompanied by a 360-degree peripheral choroidal detachment. The left fundus was remarkable only for the presence of retinochoroidal folds. Transillumination of the right eye did not show any tumor shadows, and fluorescein

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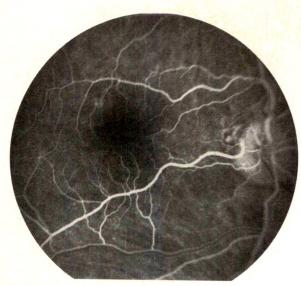


Fig. 1 (Ward and associates). Fluorescein angiography showing retinochoroidal folds.

angiography demonstrated early hyperfluorescence with no significant leakage. Results of ultrasonography were suggestive of choroidal effusion; axial length was 21 mm.

A course of 80 mg of prednisone daily was begun and the patient was referred to an internist for a complete medical examination. Results of the physical examination were unremarkable. Results of an electrocardiogram, complete blood cell count, and serum chemistries were all normal, except for a random glucose level of 157 mg/dl. A chest x-ray showed mild cardiomegaly.

Her surgical history was noteworthy for a hysterectomy for uterine carcinoma in situ without recurrence. Her medical history disclosed joint problems with right shoulder tendinitis, sciatica, and a knee disorder. Several falls had caused minimal head trauma over the previous year, but she denied syncope. She denied any alcohol or cigarette use and was taking diazepam and sulindac for bursitis. Her family history was remarkable for hyperopia in a brother and in her daughter. Both relatives had shallow anterior chambers and the brother had bilateral retinochoroidal folds. Best-corrected visual acuity was 20/20 in both eyes of both relatives.

Two months later, results of our patient's ocular examination were unchanged, and the prednisone was tapered. The choroidal folds in both eyes had persisted. Observation was continued over the next 16 months, with no signifi-

cant change in the ocular findings. By September 1980, spontaneous resolution of the choroidal folds had occurred, but residual retinochoroidal folds remained. One year later, a limited choroidal detachment returned and with no treatment waxed and waned over the next five years. Visual acuity and intraocular pressure remained stable.

In March 1986, bilateral uveal effusions were noted on examination. Ultrasonography demonstrated thickening of the retinochoroidal layers in both eyes, with nasal and temporal choroidal elevation (Fig. 2). Axial length was 21.1 mm in each eye. By May 1986, the patient complained of decreased vision in the right eye; visual acuity was 20/100. Ophthalmoscopy demonstrated a secondary inferior serous retinal detachment, with shifting fluid, and a 360degree uveal effusion in the right eye. Uveal effusions in the horizontal meridians were also noted in the left eye. Ultrasonography confirmed these findings and the patient was again given 80 mg of prednisone per day. One week later, visual acuity in the right eye improved to 20/40, but no changes in her fundus could be detected. The corticosteroids were gradually discontinued. Over the next month, visual acuity decreased to 20/60 in the right eye secondary to serous retinal detachment, and a vortex vein decompression with partial thickness sclerectomy was performed in June 1986.

The operative procedure on the right eye was performed after administration of general anesthesia. After a 360-degree limbal peritomy was

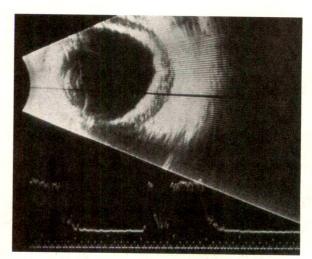


Fig. 2 (Ward and associates). Ultrasonography demonstrating thickened retinochoroidal layers with choroidal elevation.

completed, the conjunctiva and Tenon's capsule were reflected and bare sclera was exposed. On examination, the sclera was found to be extraordinarily thick. A plane of dissection was established at two-thirds scleral depth and scleral flaps 10 × 8 mm were raised in all four quadrants. These flaps extended from the equator posteriorly to the anterior portion of the vortex veins, which were dissected free. A hypoplastic vortex vein was present in each quadrant. These veins were less than one-half normal thickness and two of the vortex veins were multibranched. Neither a full-thickness sclerostomy nor suprachoroidal fluid drainage by sclerotomy was attempted. The scleral flaps were excised and the sclera was sent for light microscopy, electron microscopy, and tissue culture.

Three months after surgery, visual acuity returned to 20/30 in the right eye, the choroidal detachments had resolved, and minimal subretinal fluid remained inferiorly. The left eye continued to demonstrate a nasal and temporal choroidal detachment. Ultrasonography confirmed these findings and provided the following measurements: anterior chamber depth, R.E.: 1.81 mm and L.E.: 1.24 mm; anterior/posterior lens thickness, R.E.: 5.64 mm and L.E.: 5.58 mm; and calculated lens/eye volume ratio, 7% in each eye.

Material and Methods

Morphologic studies—Sclera for light microscopy was fixed in 10% neutral buffered formalin and then dehydrated in graded ethyl alcohol and Histoclear (xylene substitute, which is a mixture of food oil distillate). The specimen was embedded at 56 to 58 C in paraffin and sectioned. Histologic staining was completed with hematoxylin and eosin, Alcian blue, and periodic acid-Schiff.

For electron microscopy, the sclera was fixed in 2.5% glutaraldehyde for two hours, washed with 0.1 M phosphate buffer, and then transferred to 1% osmium for one hour. After washing again with phosphate buffer, the specimen was dehydrated in graded ethyl alcohol, and infiltrated and embedded in epoxy resin. Ultrathin sections were cut with a diamond knife on a microtome and double stained with uranyl acetate followed by lead citrate. Micrographs were then taken with an electron microscope.

Cell cultures—Scleral tissue obtained at sur-

gery from our patient was minced and rinsed with Hanks' solution. Scleral sections from two other control eyes were obtained less than 15 minutes after enucleation and treated in a similar fashion. One control eye had diabetic retinopathy with neovascular glaucoma and the other eye had a choroidal melanoma. Culture techniques were similar to those described previously.8 The fine scleral particles were placed in tissue culture medium (nutrient mixture F-12) with 10% fetal calf serum on 35-mm tissue culture plastic plates. These plates were placed in an incubator with 5% CO2 at 37 C. After the scleral cells had grown to confluence, the cells were scraped from the plate with a laboratory rubber scraper. The cells were collected with a pipette, centrifuged, and rinsed with Hanks' solution. The pellet was then processed for electron microscopy.

Results

Microscopy—Light microscopy of the excised sclera demonstrated irregularly arranged, interwoven bundles of collagen with varying thicknesses. The control scleras demonstrated regularly arranged collagen bundles. No inflammatory cells were observed. Alcian blue staining was observed in a diffuse pattern throughout the patient's scleral specimen. The control scleras exhibited only areas of patchy staining with Alcian blue. This finding is compatible with a greater amount of extracellular acid mucopolysaccharide in the patient's sclera compared to the control scleras. Results of periodic acid-Schiff staining were unremarkable in all specimens.

Electron microscopy of the surgical specimen demonstrated loosely and irregularly arranged collagen fibrils, fibroblasts, and degenerating blood vessels. Also present were macrophages with long slender processes containing vacuoles and phagocytizing lipid droplets. Sclera incubated with ruthenium red displayed dense extracellular staining between collagen fibers, which is consistent with the presence of acid mucopolysaccharides⁹ (Fig. 3). The diameter of the collagen fibrils ranged from 121 to 300 nm. This was consistent with the measurements of nanophthalmic scleral collagen fibrils made by other investigators. ^{10,11}

Cell cultures—Electron microscopy of the patient's scleral tissue culture cells demonstrated fibroblasts with dilated endoplasmic reticulum,



Fig. 3 (Ward and associates). Electron micrograph of segment of sclera from right eye stained with ruthenium red. Longitudinal (L) and transverse (T) sections of collagen. Dense deposits (arrows) probably represent acid mucopolysaccharides (×16,640).

as previously reported. 11 Numerous large intracellular granules of a glycogen-like substance were also observed (Fig. 4). Abnormal intracellular glycogen granules were not found in the control scleras (Fig. 5).

Discussion

Ciliochoroidal effusion has frequently been misdiagnosed as uveal melanoma. Several cases of clinically suspected ring melanomas were diagnosed as circumferential uveal effusion after enucleation.^{2,12} Ultrasonography, transillumination, and fluorescein angiography can be useful in reaching the appropriate diagnosis in these cases.

Ciliochoroidal effusion is associated with inflammation (uveitis, Vogt-Koyanagi-Harada syndrome), trauma (surgical, blunt, laser), and

systemic diseases (myxedema, multiple myeloma). 1,2,13 None of these conditions were present in our patient and the diagnosis of idiopathic uveal effusion syndrome was made, although some nanophthalmic features were found. The nanophthalmic findings included severe hyperopia, thick, irregular sclera, shallow anterior chambers, high lens/eye volume ratio, and uveal effusion. 4,6,11 The anterior chambers were extremely shallow and the axial lens thickness was increased bilaterally. The calculated lens/ eye volume ratio was 7% (normal, 3.1% to 4.4%).14 All of the above values were within the range of those for nanophthalmic eyes reported by Singh and associates.6 However, an axial length of 21.1 mm is not consistent with findings in eyes with nanophthalmos. Duke-Elder stated that the axial length of nanophthalmic eyes ranges from 16 to 18.5 mm in the anteroposterior dimension. In the largest reported series of 32 nanophthalmic eyes, axial

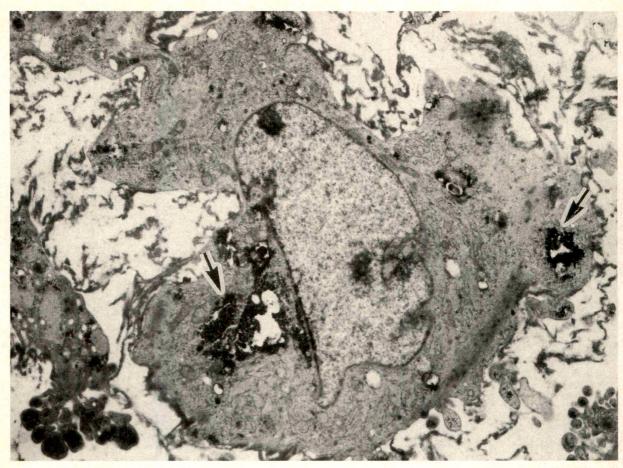


Fig. 4 (Ward and associates). Electron micrograph of cultured scleral cell from our patient. Large intracellular masses of glycogen-like granules (arrows) are present (\times 6,532).

length varied between 14.5 and 20.5 mm (median, 16.8 mm). Other reports of axial length have ranged from 15 to 20 mm. 11.13-18 Our patient's axial length of 21.1 mm is outside the upper limit of all previous reports in nanophthalmic eyes. Additionally, our patient's hyperopia of +6.50 diopters bilaterally was lower than the range (+7.25 to +20.00 diopters) reported by Singh and associates. Gass and Jallow described a patient similar to ours with idiopathic uveal effusion syndrome and small but not nanophthalmic eyes, with moderate hyperopia, thickened posterior pole choroid, and peripheral ciliochoroidal effusion.

Features of uveal effusion syndrome include ciliochoroidal effusion, abnormal sclera, dilation of episcleral blood vessels, vortex vein anomalies, a few vitreous cells, normal intraocular pressure, pigment epithelial changes, nonrhegmatogenous retinal detachment with shifting of subretinal fluid, increase of

cerebrospinal fluid protein level without pleocytosis, and a prolonged waxing and waning clinical course. 6,19 Our patient did have thickened abnormal sclera, vortex vein anomalies, normal intraocular pressure, and a waxing and waning course, which is consistent with idiopathic uveal effusion syndrome. The pigment epithelial changes and retinochoroidal folds in our patient have been described in the uveal effusion syndrome. 3,19 It has been hypothesized that choroidal folds can form whenever the sphere encompassed by Bruch's membrane is decreased, thereby causing a crimping of Bruch's membrane into folds. 20,21 This situation occurs with choroidal thickening and a rigid thick sclera, and both of these features were present. A hypothesis on the pathogenesis of the thickened sclera and uveal effusion seen in our patient can be formulated from our laboratory studies of the abnormal sclera. Electron microscopy of the sclera showed three interest-

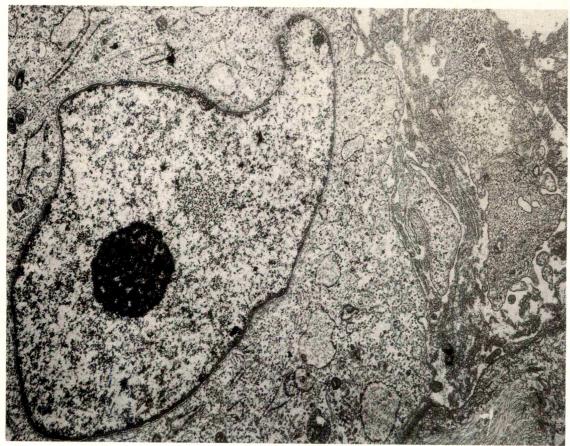


Fig. 5 (Ward and associates). Electron micrograph of cultured cell from control sclera. No abnormal glycogen deposits are evident (\times 7,457).

ing findings: (1) increased glycosaminoglycanlike deposits between the scleral fibers, (2) dilated rough endoplasmic reticulum in the scleral cells, and (3) large intracellular glycogen-like granules in the scleral culture cells.

The finding of sulfated glycosaminoglycanlike deposits confirms the previous report by Trelstad, Silbermann, and Brockhurst10 in a nanophthalmic patient. However, Yue and associates11 did not find intrascleral deposits of glycosaminoglycan either morphologically or histochemically in a nanophthalmic eye. Variations in experimental techniques or in specimens could account for these differences. Yue and associates11 cultured the scleral cells of a nanophthalmic patient and found decreased glycosaminoglycan production compared to control sclera production. No electron microscopy was done on these cells. In our case, large electron dense glycogen-like deposits were found in the cultured scleral cells. 11 No glycogen deposits were found in the scleral cultures of the two control eyes.

Although inconsistencies are evident concerning glycosaminoglycan production, all three previous studies suggest an altered glycosaminoglycogen synthesis. The intracellular glycogen-like granules found in our patient's scleral culture cells may be a cause or an effect of an altered metabolic process. Alternatively, these granules may form only in an in vitro cell culture environment. The latter probably is not true since the two control scleras did not form these granules in cell culture. Previous research implies that glycosaminoglycan composition controls the organization and size of the collagen fibers in the cornea and sclera. 22 Therefore, abnormal glycosaminoglycan production, either in quantity or in type, may play a direct role in the formation of abnormally thick sclera. Additional research in this area is needed to clarify these relationships.

The pathogenesis of choroidal and subretinal

fluid is probably related to the presence of the abnormally thick sclera, as previously hypothesized by Gass.3 The thickened sclera may act as a relative barrier to the diffusion of suprachoroidal fluid and colloids out of the globe. Protein, especially albumin, enters the suprachoroidal space by molecular sieving from the choroidal vessels.²³ Since no lymphatic system exists within the eye, the proteins are either reabsorbed into the choroidal vascular system, flow outward by a pressure gradient through the sclera, or enter the anterior chamber to leave via Schlemm's canal. Neither protein pumps nor protein enzymatic breakdown has been demonstrated in the choroid or sclera.24 Therefore, it is postulated that a significant proportion of the protein must be flushed from the eye by transscleral diffusion with the suprachoroidal fluid outflow. 3,24-26 The presence of thick sclera may represent a potential outflow barrier. The protein concentration would gradually increase in the suprachoroidal fluid and the oncotic choroidal tissue pressure would increase, causing additional fluid to transude from the choroidal vasculature.27 Fluid and protein accumulation may cause the choroid to become thickened. The abnormal sclera, which is now further thickened by edema and extracellular colloid, might then impinge upon and compromise both vortex veins and emissarial channel drainage.⁸ Clinically recognized ciliochoroidal effusion would eventually occur.

Chronic ciliochoroidal effusion might cause a decompensation of the retinal pigment epithelium and allow the proteinaceous fluid to pass into the subretinal space.³ The retinal pigment epithelium pumps the influx of fluid from the subretinal space, but since water is removed without proportional protein shift, the protein concentration rises in the subretinal fluid.^{3,28-30} A bullous shifting retinal detachment ensues.

The rationale for treatment of uveal effusion and the attendant nonrhegmatogenous retinal detachment has evolved over the past few years as the pathogenesis of this condition has been better defined. In 1974, Brockhurst¹⁶ reported five cases of nanophthalmos with uveal effusion and recommended that both glaucoma and retinal detachment surgical procedures be avoided if possible. Subsequently, Shaffer³¹ hypothesized that the thickened sclera impaired venous outflow, causing uveal effusion in nanophthalmos. In a follow-up report, Brockhurst¹³ described ten cases of uveal effusion and nonrhegmatogenous retinal detachment in nanophthalmic eyes that were surgically treat-

ed with vortex vein decompression and sclerotomies. Subretinal fluid drainage was also done in some cases. Eight of the ten patients had successful reattachment of the retina. A similar technique was successfully used by Yue and colleagues. 11

In 1983, Gass³ raised a lamellar scleral flap, avoiding the exit sites of the vortex veins. He then placed a sclerostomy within the lamellar scleral bed, leaving the choroid exposed for continuous drainage of suprachoroidal fluid. This technique proved successful.

In our case the surgical technique was modified. Paralleling the operative procedures of Brockhurst and Gass, a two-thirds thickness lamellar scleral flap was raised, exposing and decompressing the vortex veins, in four quadrants. However, no full-thickness sclerotomy or sclerostomy was made, and neither direct suprachoroidal nor subretinal fluid drainage was performed. Postoperatively, the subretinal fluid resolved completely after three months and ciliochoroidal effusion decreased.

This successful result seems to confirm the hypothesis that scleral/emissarial channel impermeability or vortex vein obstruction, or both, were the causes of the uveal effusion and the serous retinal detachment. The diffusion barrier of the sclera was removed without the aid of a sclerotomy or a sclerostomy.

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Repeated Fluid-Gas Exchange for Hypotony After Vitreoretinal Surgery for Proliferative Vitreoretinopathy

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Three patients with prolonged hypotony after vitreoretinal surgery for proliferative vitreoretinopathy were treated with repeated fluid-gas exchanges to maintain intraocular pressure and prevent the development of phthisis bulbi. We performed fluid-gas exchanges solely to treat the hypotony beyond the period when tamponade of retinal breaks was required, and without specific positioning of the bubble. In these patients, the intraocular pressure eventually returned to normal and useful vision was retained.

Persistent hypotony is common after vitreoretinal surgery for complex retinal detachments with proliferative vitreoretinopathy. In a series of patients with proliferative vitreoretinopathy, Gonvers1 used silicone oil as a temporary tamponade and found, after its removal from 90 successfully treated eyes, that 18 (20%) had final intraocular pressures of 1 to 5 mm Hg. An additional six eyes had an intraocular pressure of 0 mm Hg and collapsed posterior poles. Presently, Gonvers believes that such eyes with pressures of 3 mm Hg or less will progress to phthisis bulbi if the silicone oil is removed (written communication, March 5, 1988). Machemer, McCuen, and de Juan² also commented that silicone oil tamponade may prevent phthisis bulbi in hypotonous eyes with large retinectomies and attached retinas. Additionally, Lewis and associates3 did not remove silicone oil in some cases of proliferative vitreoretinopathy with anterior traction to prevent phthisis bulbi.

We treated three patients with prolonged

hypotony that developed after successful surgery for severe proliferative vitreoretinopathy with repeated fluid-gas exchanges to maintain intraocular pressure because of the risk of ocular collapse and subsequent phthisis bulbi. We performed the fluid-gas exchanges beyond the period when tamponade of retinal breaks was required. In these patients, intraocular pressure eventually returned to normal, with the retention of useful vision. The patients described represent our only experience using this technique for hypotony.

Case Reports

Case 1

A 62-year-old man with decreased vision in the left eye for three to four weeks was found to have a retinal detachment with a giant retinal tear and a rolled posterior edge extending from the 12:30 to the 5:30 meridians temporally. The macula was detached and visual acuity was counting fingers. In August 1986, the patient underwent cryopexy, vitrectomy without lensectomy, and a total fluid-gas exchange with 5% sulfur hexafluoride in the left eye. After surgery the retina was reattached. Three weeks later, we noted a total detachment caused by proliferative vitreoretinopathy, with severe fixed folds secondary to periretinal membranes in all quadrants, and performed a lensectomy, repeat vitrectomy, scleral buckle, and total fluid-gas exchange (with 35% sulfur hexafluoride), as well as internal drainage through a small posterior retinotomy to reattach the retina. We applied cyanoacrylate adhesive externally at the end of surgery to stop persistent leakage from the two superior sclerotomy sites after initial closure with sutures. Two weeks later we performed a partial fluid-gas exchange with 100% sulfur hexafluoride for extended tamponade of the retinal breaks for only one more week.

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By the following week, the patient's eye was hypotonous (pressure by applanation tonometry was 2 mm Hg). There was no evidence of leakage from the sclerotomy sites. We then performed a total fluid-gas exchange to prevent collapse of the eye. Over the next three months, although the retina remained attached, we performed four additional outpatient partial fluid-gas exchanges (three with 30% to 100% sulfur hexafluoride and one with 15% perfluoropropane) in an attempt to overcome the hypotony when the pressure was below 3 mm Hg (Fig. 1). Ten weeks postoperatively, we removed the exposed cyanoacrylate. This had no effect on intraocular pressure. At the most recent follow-up examination, 17 months after the second surgery, visual acuity was 20/200 and the retina was attached with no residual gas. Intraocular pressure was 9 mm Hg. On gonioscopy, we observed the trabecular meshwork and scleral spur for 360 degrees and noted no synechiae.

Case 2

This 44-year-old woman was first examined by us in April 1987 for a recurrent retinal detachment and proliferative vitreoretinopathy. She had a history of severe myopia and a visual acuity of no light perception in the right eye secondary to phthisis bulbi from a previous complicated retinal detachment for which she never had surgery. The patient's daughter also had a history of retinal detachment and severe myopia.

In March 1987, visual acuity was 20/80 in the left eye because of a moderately dense nuclear sclerotic cataract. The patient underwent extracapsular cataract extraction without intraocular lens implantation. Two months earlier, in anticipation of this procedure, she had prophylactic transconjunctival cryotherapy because of multiple areas of lattice degeneration associated with retinal breaks. The day after cataract surgery, localized superonasal and inferotemporal rhegmatogenous retinal detachments developed and the patient was treated with a scleral buckle.

Postoperatively, the retina remained attached for one month and visual acuity improved to 20/30. When we initially saw the patient in April 1987, visual acuity was counting fingers at 1 foot and the retina had redetached because of proliferative vitreoretinopafixed folds with and periretinal membranes in both temporal quadrants. We then performed a pars plana vitrectomy with dissection of epiretinal membranes, a relaxing retinotomy temporally, revision of the scleral buckle, fluid-gas exchange with 15% perfluoropropane, and argon endophotocoagulation. The retina was successfully reattached.

Four weeks postoperatively, the retina redetached, with recurrent inferior proliferative vitreoretinopathy and anterior traction from a membrane adherent to the back of the iris, inferior pars plana, and adjacent retina. In July 1987, we performed a repeat vitrectomy, a large inferonasal retinectomy and iridectomy, and a

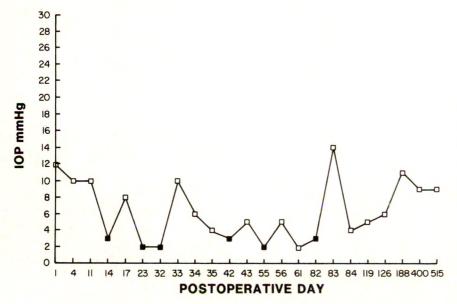


Fig. 1 (Stallman and Meyers). Case 1. Intraocular pressure plotted by postoperative day. For clarity of illustration, only representative pressure measurements are plotted. IOP, intraocular pressure; solid boxes, times of fluid-gas exchanges.

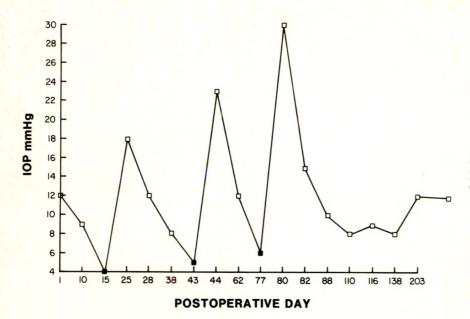


Fig. 2 (Stallman and Meyers). Case 2. Intraocular pressure plotted by postoperative day.

total fluid-gas exchange with 18% perfluoropropane. Over the following three months, the patient had three additional outpatient fluidgas exchanges to relieve persistent hypotony when intraocular pressure was less than 6 mm Hg (Fig. 2). The first two of these fluid-gas exchanges were complete. We noted small subretinal gas bubbles under the elevated edge of the retinectomy after the last two fluid-gas exchanges, but this did not cause progressive redetachment. Immediately after the second fluid-gas exchange (six weeks postoperatively), we discontinued positioning for tamponade and the retina remained attached except for an area of proliferative vitreoretinopathy superonasally, anterior to the posterior crest of the buckle. The gas completely reabsorbed 41/2 months after the last surgery and intraocular pressure gradually increased to 12 mm Hg by 8½ months after the last surgery. On gonioscopy, we observed 40% of the angle open to the scleral spur, with the remainder closed by synechiae. At that time, best-corrected visual acuity was 20/80.

Case 3

A 26-year-old man sustained blunt trauma to the right eye on July 21, 1987. According to the referring ophthalmologist, he had a total hyphema, a 13-mm scleral laceration that extended radially from the corneoscleral limbus in the 6 o'clock meridian, and vitreous prolapse through the wound. The ophthalmologist

closed the wound after disinserting the inferior rectus muscle but did not perform a vitrectomy.

The patient was referred to us on July 30, 1987. Visual acuity was light perception with color perception. There was a 1+ reverse afferent pupillary defect, moderate corneal edema, and an 80% hyphema. Intraocular pressure by applanation tonometry was 2 mm Hg. Visualization of the posterior segment was not possible. Ultrasonography showed a shallow anterior chamber, multiple vitreal membranes, and 360-degree choroidal and ciliary body thickening.

The hyphema partially cleared over the next month, disclosing traumatic aniridia, a subluxated lens, and a vitreous hemorrhage. Moderate central corneal blood staining had developed. Repeat ultrasonography demonstrated resolution of the choroidal thickening, a posterior vitreous detachment, and a localized retinal detachment inferiorly.

On Sept. 18, 1987, we performed a lensectomy, vitrectomy with a scleral buckle, and fluidgas exchange with 20% perfluoropropane. At surgery, we noted an inferior retinal detachment with severe proliferative vitreoretinopathy and a single break at the 5:30 meridian near the ora serrata. Postoperatively, the retina was reattached. Intraocular pressure was initially 40 mm Hg but decreased to 15 mm Hg over several days. On postoperative day 17, intraocular pressure was 2 mm Hg and choroidal detachments developed from the 10 to the 2

o'clock meridians. We could not identify any microcystic change in the conjunctiva over the sclerotomy sites to suggest inadvertent filtration. On the same day, the patient underwent an outpatient partial fluid-gas exchange with 40% perfluoropropane but was not positioned for retinal tamponade. This raised the pressure only for a few days. The retina remained attached.

Over the next three months, we performed three more fluid-gas exchanges on an outpatient basis to prevent ocular collapse when the intraocular pressure was less than 3 mm Hg (Fig. 3). An acute pressure rise (56 mm Hg) occurred two days after one of the partial fluid-gas exchanges, requiring partial removal of the gas. Four months postoperatively, intraocular pressure was 7 mm Hg, visual acuity was 20/200, and about a 15% gas fill remained. The retina remained attached except for residual areas of proliferative vitreoretinopathy anterior to the posterior crest of the buckle and a membrane over the ciliary body for nearly 360 degrees.

The patient was last seen seven months after surgery, at which time intraocular pressure by applanation tonometry was R.E.: 11 mm Hg and L.E.: 14 mm Hg. On gonioscopy, we observed diffuse synechiae and fibrosis with approximately one third of normal-appearing angle open to the scleral spur in the right eye.

The posterior segment was unchanged and best-corrected visual acuity was 20/200.

Material and Methods

We performed fluid-gas exchanges when intraocular pressure by applanation tonometry measured less than 3 mm Hg in Cases 1 and 3 and less than 6 mm Hg in Case 2. Because of the thin sclera and low scleral rigidity observed at surgery in Patient 2, we did not want the pressure to fall below 5 mm Hg to avoid ocular collapse in the patient's only eye. We used the Goldmann applanation tonometer to measure intraocular pressure, as it is more accurate than the Schiøtz tonometer in gas-filled eyes.⁴

In Patient 3 and during the second vitrectomy in Patient 2, we placed all three sclerotomies 3.5 mm from the corneoscleral limbus in the superior 150 degrees of the pars plana, with the infusion cannula near the 12 o'clock meridian. We used this technique to avoid the hole at the inferotemporal sclerotomy site, which may be responsible for some recurrent inferior detachments of the pars plana and retina in patients with severe inferior proliferative vitreoretinopathy. This did not interfere with the surgery. In Case 1, the infusion cannula was in the inferotemporal quadrant.

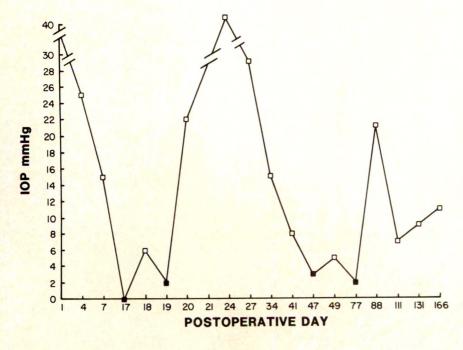


Fig. 3 (Stallman and Meyers). Case 3. Intraocular pressure plotted by postoperative day.

After vitrectomy, all three patients received 60 mg of oral prednisone for five days and topical corticosteroids four times a day for two to three months. When examination showed only minimal cell and flare, the corticosteroids were tapered and discontinued.

We initially used sulfur hexafluoride for fluid-gas exchanges but later switched to perfluoropropane when it became available to us because of its slower absorption from the eye. The concentration of perfluoropropane used varied as we gained experience with it. We performed fluid-gas exchanges intending to produce or maintain an initial intraocular pressure above 10 mm Hg. The percentage gas fill (by volume) required to achieve this varied widely. We performed the fluid-gas exchanges using a two-needle method to achieve a complete gas fill in aphakic eyes. We positioned the patient face down and instilled a topical anesthetic (proparacaine) and topical antibiotic (gentamicin) preoperatively. Occasionally, we used retrobulbar anesthesia. In aphakic eyes, we entered the corneoscleral limbus at the 3 and the 9 o'clock meridians with two 30-gauge, ½-inch needles, one angulated to about 110 degrees and one angulated to 90 degrees. We attached the 110-degree angulated needle via a long flexible polyethylene tube to the syringe of gas, held by an assistant. The gas had been filtered through a double Millipore filter. We attached the 90-degree angulated needle to a similar tube draining to gravity. The surgeon inserted both needles using an indirect ophthalmoscope for illumination. For augmentation of an existing bubble or partial fluid-gas exchange, we used a single needle and syringe technique, with the patient seated as previously described. 6-11

We find the use of flexible tubing to be advantageous in the two-needle technique because any movement of the assistant on the plunger of the syringe is not transmitted to the needle in the eye as it is through a rigid syringe. We therefore obtain better fingertip control and avoid repeated manipulation of the needle with respect to the entry site as is required with other techniques. Access to the dependent fluid is more direct and possibly safer. Additionally, there should be no transient fluctuations of intraocular pressure as injection is not alternated with aspiration and egress of fluid is passive. Not applying active suction to the syringe may reduce the risk of iris or vitreous strand incarceration, although this rarely occurs. 6 Liabilities of this technique include the

need for two puncture sites, the need for prone positioning, and the formation of small bubbles if the injection needle cannot be positioned within an existing bubble. Corneal endothelial touch is possible if attempts to remove the last drop of fluid are too aggressive. For many elderly or frail patients or those where only a partial gas fill is desired, however, the single needle technique may be more appropriate.

Results

Complications of gas injection included one acute rise in intraocular pressure (to 56 mm Hg) two days after a partial fluid-gas exchange in Case 3; this required paracentesis and partial removal of gas. Trabecular outflow must have been compromised in this patient, since the anterior chamber angle was severely damaged from the trauma. Patient 2 developed small subretinal gas bubbles under the edge of the retinectomy, but this did not adversely affect the outcome. Potential complications of multiple punctures such as endophthalmitis, iridodialysis, and corneal decompensation did not occur in our patients.

No instances of iridocorneal adhesion occurred after fluid-gas exchange in our three patients.

Discussion

Eyes with severe and persistent hypotony following extensive vitreoretinal surgery are at risk of developing phthisis bulbi. Besides silicone oil, there has been one report of repeated injections of sodium hyaluronate (Healon) for hypotony over a five-year period in a patient with chronic uveitis. The authors showed a consistent relationship between the injections and increases in intraocular pressure as well as improvements in visual acuity. We elected to use long-acting gases to avoid the potential complications of silicone oil.

Repeated fluid-gas exchanges may be performed to maintain prolonged tamponade of retinal breaks as an alternative to silicone oil in selected cases. ⁶⁻¹¹ During the early postoperative period, the gas certainly served this purpose in our cases. Thereafter, we discontinued positioning and used the repeated gas injections solely to counteract hypotony.

We postulate several mechanisms that may have contributed to the hypotony in these cases. Although there is some debate, 18,14 studies with vitreous fluorophotometry have demonstrated that there is likely to be aqueous humor outflow through retinal breaks, and this may be responsible for the decreased pressure often seen with uncomplicated retinal detachments. 15 In eyes with large areas of bare retinal pigment epithelium after retinectomies or giant tears, this outflow pathway may be significant.2 Other studies have suggested that the decreased pressure may be secondary to outflow of aqueous humor through the juxtapapillary connective tissue and into the optic nerve sheath in simple detachments extending to the disk. 16 This route of egress would be available only in eyes with a persistent posterior retinal detachment postoperatively.

After extensive surgery for severe proliferative vitreoretinopathy, ciliary body shutdown is probably a major factor in causing severe hypotony, as the intraocular pressure in eyes with uncomplicated detachments is reportedly only 2.7 to 3.5 mm Hg lower than that in the contralateral eye.14 A subclinical ciliary body detachment may have contributed to the hypotony in Case 3, since there was a mem-

brane present over the ciliary body.

An additional possibility is that there was transient leakage from sclerotomy sites after vitrectomy. We carefully examined the conjunctiva for evidence of leakage, especially in Patient 1, who required external cyanoacrylate adhesive intraoperatively, but we saw no leakage. Even if there were subclinical leakage from the sclerotomy sites, this should have been minimized by the gas blocking these openings, since they were placed superiorly in Patients 2 and 3. The pressure remained low even when the gas fill was greater than 50%.

There are several possible mechanisms by which fluid-gas exchange temporarily restores near-normal intraocular pressure in hypotonous eyes. These include rotation of the iris with partial or complete angle closure, especially in the supine position, and expansion of the gas in an already gas-filled eye.4 Alternatively, the gas bubble might occlude the outflow of an anatomically deep anterior chamber angle. The cells and flare frequently noted after fluid-gas exchange could also contribute to blockage of trabecular outflow.

In our cases, where a normal intraocular pressure was eventually restored and maintained without gas, we hypothesize that the ciliary body recovered adequate secretory function and the eyes averted collapse because of the presence of gas. In Cases 2 and 3, trabecular obstruction may have altered the balance between inflow and outflow, although its contribution is difficult to quantitate. Further, we cannot evaluate whether there was progression of angle closure in these cases, because initial gonioscopy was not performed when the eyes were gas filled or hypotonous.

Patients who undergo repeated gas injections for hypotony require frequent follow-up (sometimes on a daily or weekly basis) and a major time commitment. The potential for vision and overall physical condition of the patient must

be considered.

The severely hypotonous eyes in this study may have eventually recovered without the use of gas. However, we believe these eyes were at high risk for developing phthisis bulbi and might not have recovered if allowed to collapse. Since the natural course of prolonged hypotony in similar cases is not known, a prospective randomized study is needed but will be difficult to accomplish because of the many variables in these complex cases.

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OPHTHALMIC MINIATURE

"Close her eye," said Maud, gripping my hand as if she felt herself still in the wild river. "You must never let the dead look at you."

I dutifully moved the eyelid down over the eye, feeling the flesh soft, pliable, and without warmth, but not yet chilled, somewhat like the loose skin of a chicken dead thirty minutes.

"What can the dead see?" I asked Maud when I'd done her bidding.
"If you look in their eyes you see your fate. And one must never know one's fate if one is to keep sane."

William Kennedy, *Quinn's Book* New York, Viking Penguin Inc., 1988, p. 17

Pseudoinflammatory Macular Dystrophy

R. F. Dreyer, M.D., and Ahmed A. Hidayat, M.D.

We studied a family with a dominantly inherited macular dystrophy resembling Sorsby's pseudoinflammatory dystrophy. Retinal pigment epithelial atrophy and varying degrees of pigment epithelial metaplasia were prominent fundus features in this pedigree. However, findings on electro-oculography were abnormal, unlike previous findings in patients with Sorsby's dystrophy. Histopathologic study of an eye from one patient demonstrated widespread atrophy of the retina, retipigment epithelium, and choroid. Although the pseudoinflammatory fundus appearance is common to several macular dystrophies and some eyes with end-stage, agemacular degeneration, abnormal electro-oculograms and a dominant inheritance pattern distinguish the dystrophy in the present pedigree from other dystrophies and age-related macular degeneration.

Sorsby's Dystrophy is an autosomal dominant condition in which atrophic lesions of the pigment epithelium and choroid develop. 1-4 In some patients, whose symptoms began around 40 years of age, the atrophy was preceded by retinal edema and hemorrhage, with lesions first appearing in the posterior pole and extending into the periphery. Hoskin, Sehmi, and Bird⁵ later extended the pedigree study of Sorsby, Mason, and Gardener, confirming their original findings of a bilateral process initially involving the macular region, with peripheral loss occurring late in some patients. They identified bilateral fine drusen in three patients and bilateral angioid streaks in two patients. In two patients, a yellow subretinal deposit was also identified. In electrophysiologic studies of some patients at risk for carrying the abnormal gene but with normal vision, they found no electrophysiologic abnormalities. Carr, Noble, and Nosaduke⁶ studied four individuals from a pedigree in which pseudoinflammatory macular dystrophy had been diagnosed. Results of electro-oculograms and electroretinograms were normal in two patients. They suggested the condition be termed hereditary hemorrhagic dystrophy, emphasizing that some patients develop subretinal hemorrhage secondary to choroidal neovascular membranes.

Ashton and Sorsby⁷ described histopathologic findings from two sisters included in the original study by Sorsby, Mason, and Gardener. 1 No family members of these sisters had decreased vision; therefore, autosomal dominant inheritance was not demonstrated in this pedigree. In both patients, they found marked atrophy of the retinal pigment epithelium with sclerosis of the choriocapillaris and large choroidal vessels. Breaks in Bruch's membrane and choroidal neovascular membranes were also identified. One of the two patients had drusen. This report of histologic findings which resembled age-related macular degeneration blurred the distinction between Sorsby's dystrophy and age-related macular degeneration.

In the present study, clinical, histologic, and electrophysiologic evidence identified a new dystrophy distinct from the above dystrophies and age-related macular degeneration, even though fundus findings occasionally resembled those of age-related macular degeneration.

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The opinions or assertions contained herein are the private views of the authors and should not be construed as being official or representing the views of the Department of the Army or the Department of Defense.

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Case Reports

Case 1

A 45-year-old man (IV-5) had paracentral scotomas for five years. The scotomas were

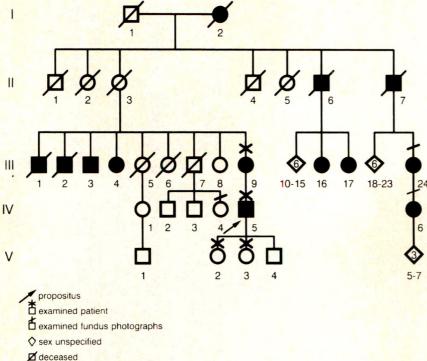


Fig. 1 (Dreyer and Hidayat). Pedigree demonstrating autosomal dominant inheritance pattern, with either incomplete penetrance or variable expressivity in Patient II-3.

- O normal male or female
- ■. affected male or female

stable until age 44 years, at which time they increased in size. His medical history was unremarkable and he was taking no medications. Many members of his family had experienced loss of vision (Fig. 1).

Visual acuity was R.E.: 20/20 – and L.E.: 20/20. There was a small, right relative afferent pupillary defect (less than 0.3 log unit). Results of slit-lamp examination of the anterior segments were unremarkable. Intraocular pressure was normal. There were no vitreous inflammatory cells and no degenerative vitreous changes in either eye. Ophthalmoscopy of the right eye showed areas of pigment epithelial and choriocapillaris atrophy, through which deep choroidal vessels could be seen. Other areas of increased pigmentation were also present. A ring of pigment epithelial metaplasia surrounded the fovea. No drusen were identified. The pigment epithelial atrophy extended beyond the arcades but not to the far periphery (Fig. 2, top left). Ophthalmoscopy of the left eye showed similar changes in the pigment epithelium and choroid (Fig. 2, top right). The optic disk and vessels were normal in both eyes.

Fluorescein angiography (Fig. 3) demonstrat-

ed several areas of total atrophy of the choriocapillaris. There was no evidence of a choroidal neovascular membrane. A zone of early hyperfluorescence with late fading surrounded each fovea, corresponding to areas of retinal pigment epithelial metaplasia and atrophy. The amplitude of the scotopic electroretinographic B-wave was 326 mV in the right eye and 336 mV in the left eye. This was slightly greater than one standard deviation below normal for this laboratory. The electro-oculogram recorded a light:dark ratio of 1.1:1 in the right eye and 1.6:1 in the left eye (normal ratios for this laboratory are 1.4:1 to 2.6:1).

Case 2

The 78-year-old mother (III-9) of Patient 1 first noted reduced vision in her 30s. The right eye was affected first, and the left eye was affected at age 39 years. At age 40 years, the patient was examined by an ophthalmologist who noted "marked grayish areas in front of degeneration" in both eyes. At age 64 years, visual acuity was R.E.: hand motions and L.E.: 20/70. At age 74 years, the patient was reexamined by another ophthalmologist who noted marked retinal pigment epithelial changes in

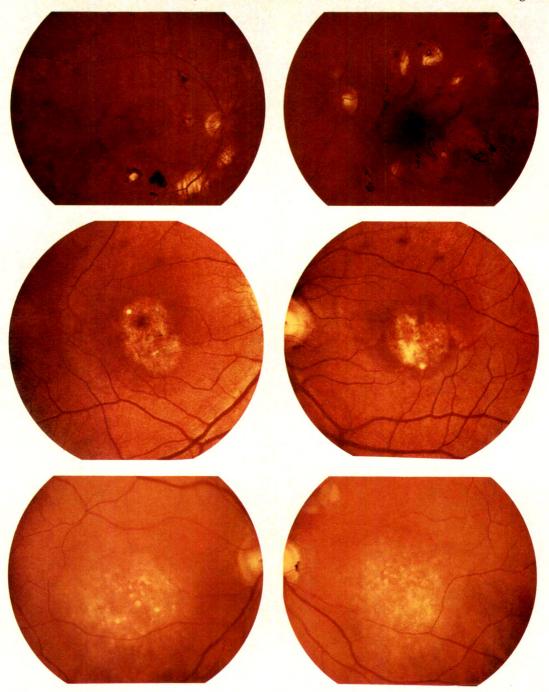
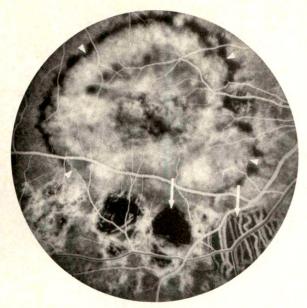


Fig. 2 (Dreyer and Hidayat). Top left, Right fundus of Patient IV-5 demonstrating a central zone of pigment epithelial metaplasia with variable atrophy of pigment epithelium, choriocapillaris, and large choroidal vessels. Top right, Left fundus of Patient IV-5 showing a central zone of retinal pigment epithelial metaplasia with more peripheral areas of pigment epithelial atrophy. Middle left, Right fundus of Patient IV-6 showing a central zone of pigment epithelial atrophy with drusen. Middle right, Left fundus of Patient IV-6 demonstrating a central zone of pigment epithelial atrophy with drusen. Note the placoid yellow subretinal deposit just above the optic disk. Bottom left, Right fundus of Patient III-24 showing atrophy of the retinal pigment epithelium in the fovea with a single drusen-like deposit above the fovea. Just below the fovea, small areas of pigment epithelial hypertrophy or hyperplasia are present. A large zone of mild pigment epithelial atrophy surrounds the more prominent central area of atrophy, with islands of preserved retinal pigment epithelial atrophy in the fovea and several small drusen-like deposits within this area. The white tissue inferonasal to the foveal center probably represents pigment epithelial metaplasia. Over a broad area surrounding this central zone of atrophy, there is mild pigment epithelial atrophy and mottling. Islands of preserved pigment epithelial atrophy are present within this broader zone of pigment epithelial loss.



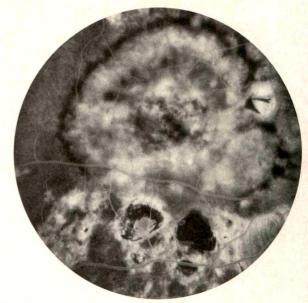


Fig. 3 (Dreyer and Hidayat). Patient IV-5. Left, Laminar flow phase fluorescein angiogram of left fundus. The area of central hyperfluorescence corresponds to the central zone of pigment epithelial metaplasia, with a surrounding ring of clumped pigment that blocks fluorescence (arrowheads). Large choroidal vessels can be seen through areas of pigment epithelial atrophy, while clumped pigment blocks fluorescence elsewhere (arrows). Right, late phase fluorescein angiogram of same eye demonstrating no leakage from the central hyperfluorescent zone, indicating that this area is not a large, inactive choroidal neovascular membrane.

both eyes. Visual acuity in the right eye was unchanged, but it had decreased to 20/100 in the left eye. The patient subsequently developed increased intraocular pressure and severe pain in the right eye, which could not be controlled medically. The eye was enucleated. Since that time, the patient has noticed a slow loss of vision in the left eye. At the initial examination at our institution at age 78 years, visual acuity was 20/400. A prominent nuclear sclerotic cataract was noted. Ophthalmoscopy showed a perifoveal area of retinal pigment epithelial atrophy surrounded by clumped retinal pigment epithelium, but no drusen were identified. The vitreous was clear of inflammatory cells. The scotopic electroretinographic B-wave measured 250 mV (2 S.D. below normal) and the electro-oculogram had no light rise.

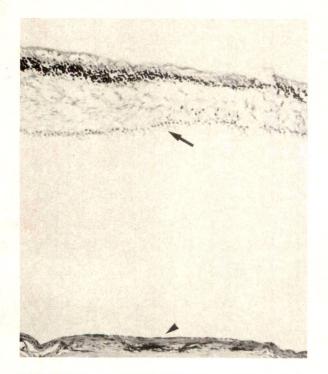
Other Family Members

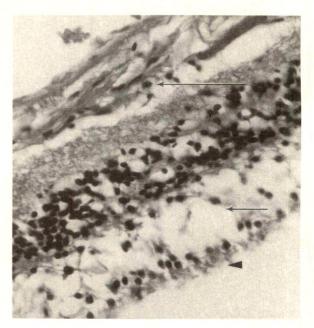
The following patients were not examined by us, but ophthalmic histories were obtained through interviews and correspondence with patients' relatives and ophthalmologists. Patient I-2 lost ambulatory vision in her 60s. The mother (II-3) and father of Patient III-9 had no known ocular disease. The mother died at age

49 years, and the father died in his 70s. Patient III-1 lost reading vision in his 60s or 70s. Patient III-2 lost reading vision in his 40s. Patient III-3, at age 74 years, could read only large-print material. Patient III-4 could read large-print materials with difficulty at age 72 years. Patient III-7 was not affected when he died at age 74 years. However, he had one daughter (IV-4) who had mild visual loss. Photographs of her fundi demonstrated drusen only.

Patients II-6 and II-7 had visual loss beginning in adulthood. Patient II-6 had two affected daughters, although the extent of their visual loss is not known. Patient II-7 had one affected daughter (III-24) who first noticed reduced distance vision at age 37 years and then failed a vision test for her driver's license at age 38 years. Visual acuity at age 76 years was 20/300 in both eyes. Fundus photographs demonstrated a broad area of retinal pigment epithelial atrophy in her right fundus, with several drusen (Fig. 2, middle left), and a similar area of atrophy in her left eye (Fig. 2, middle right).

Patient IV-6 had visual loss beginning in adulthood. Fundus photographs of the right eye showed retinal pigment epithelial atrophy centered in the fovea, with a drusen-like deposit just above the fovea. A large area of less





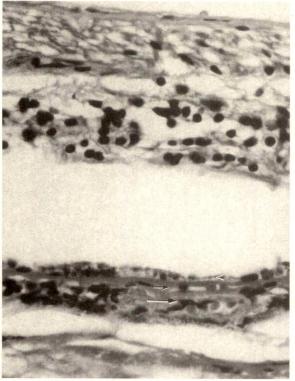


Fig. 4 (Dreyer and Hidayat). Patient III-9, right eye. Top left, Low power histologic section through macula of right eye. There is marked atrophy of all layers of the retina (arrow) as well as of the retinal pigment epithelium and choroid (arrowhead). The retina is artifactitiously detached (hematoxylin and eosin, ×50). Top right, High power histopathologic section further from fovea than in previous section. There is severe atrophy of outer segments (arrowhead). Note cystic degeneration of the outer nuclear and outer plexiform layers (short arrow) and loss of ganglion cells (long arrow) (hematoxylin and eosin, ×480). Bottom left, Histologic section through the equator of the eye. There is marked atrophy of all retinal layers, retinal pigment epithelium (arrowhead), choriocapillaris (short arrow), and large choroidal vessels (long arrow). Bruch's membrane is thickened (hematoxylin and eosin, $\times 300$).

severe pigment epithelial atrophy surrounded the fovea and several preserved islands of pigment epithelium were noted (Fig. 2, bottom left). Ophthalmoscopy of the left eye showed prominent pigment epithelial atrophy in the

fovea, with a surrounding zone of less extensive pigment epithelial atrophy extending outside the superotemporal arcade. Several drusen-like deposits were noted in the severe pigment epithelial atrophy. Within this broad-

er zone of atrophy, three preserved islands of pigment epithelium remained. Fibrous metaplasia of the pigment epithelium was present within the central zone of atrophy (Fig. 2, bottom right). The electro-oculogram had a light:dark ratio of 1.37:1 in the right eye and 1.27:1 in the left eye. This family history is summarized in Figure 1.

Histologic Findings

The right eye of Patient 2 was studied at the Armed Forces Institute of Pathology. Atrophy of the inner layers of the retina was present in the posterior pole and midperiphery. The optic nerve was atrophic, consistent with the history of acute glaucoma. However, outer photoreceptor atrophy in the macula and periphery could not be explained by glaucoma (Fig. 4). Marked atrophy of the choriocapillaris, large choroidal vessels, and pigment epithelium was present in the posterior pole and midperiphery. Bruch's membrane appeared thickened and calcified, but drusen were rare. There were no breaks in Bruch's membrane and no choroidal neovascularization.

Discussion

A pseudoinflammatory fundus appearance and drusen, or drusen-like deposits, can be seen in at least four different disease processes (Table). Sorsby, Mason, and Gardener1 were the first to recognize this appearance and named it Sorsby's dystrophy. Carr, Noble, and Nosaduke6 then renamed it hereditary hemorrhagic dystrophy to better characterize its features of subretinal neovascularization and hemorrhage, followed by hyperplasia, metaplasia, and atrophy of the pigment epithelium resembling a pseudoinflammatory process. Forsius and colleagues8 described a second pseudoinflammatory dystrophy with recessive inheritance. In addition to posterior pseudoinflammatory lesions, their patients occasionally had peripheral albinotic fundus lesions and extensive hyaline bodies in the retina that appeared similar to punctata albescens retinopathy. Mild electro-oculogram abnormalities were identified in five of ten eyes. A third condition was identified as North Carolina dystrophy. While not usually considered a pseudoinflammatory dystrophy, it sometimes causes coloboma-like macular lesions with variable retinal pigment epithelial atrophy, hypertrophy, and metaplasia at the margin of the lesion. Drusen have been reported in affected family members, and Gass¹⁰ noted that the drusen-like appearance may be caused by focal pigment epithelial atrophy. Finally, some eyes with advanced age-related macular degeneration contain drusen and disciform scars with hypertrophic and metaplastic pigment epithelium, mimicking previous inflammation.

The present dystrophy seems to be distinct from the conditions listed above. It is unlike the disease reported by Sorsby, Mason, and Gardener, and Carr, Noble, and Nosaduke, since no family members were identified with subretinal hemorrhage or choroidal neovascularization. Furthermore, Carr, Noble, and Nosaduke⁶ found normal electro-oculograms in two of four patients studied, whereas the results of electrooculography in our patients were abnormal. Hoskin, Sehmi, and Bird⁵ studied normal members of a family with a pseudoinflammatory dystrophy and found no electro-oculographic abnormalities. It may be that the pseudoinflammatory appearance is a common phenotypic expression for two dominant macular dystrophies, one with and one without abnormal electro-oculographic findings. The present dystrophy was dominantly inherited and was distinct from the recessive condition described by Forsius and colleagues.8

The present pseudoinflammatory dystrophy seems distinct from North Carolina dystrophy in which patients lose vision at an earlier age, changes are confined to the posterior pole, and results of electrophysiologic studies are almost always normal. In the present pedigree, visual loss began in adulthood, with extensive retinal pigment epithelial change occasionally extending outside the posterior pole, abnormal results on electrophysiologic studies, and no coloboma-like atrophy of pigment epithelium.

The present condition also seems distinct from age-related macular degeneration for several reasons. First, histopathologic findings from Patient 2 are remarkable for atrophy of the choriocapillaris, large choroidal vessels, and pigment epithelium. Degeneration of all retinal layers was also present both in the macula and periphery. Although a rare drusen was identified, the extramacular pigment epithelial and choroidal atrophy were unlike those seen in age-related macular degeneration. Second, abnormal electro-oculograms were recorded in three patients. In Patient IV-5, a severely abnormal electro-oculogram was recorded in the right eye and a low-normal electro-oculogram was recorded in the left eye, both with a minimally reduced electroretinogram. In Patient 2

TABLE
A COMPARISON OF DYSTROPHIES WITH A PSEUDOINFLAMMATORY FUNDUS APPEARANCE
AND DRUSEN-LIKE DEPOSITS

DYSTROPHY	INHERITANCE	AGE OF ONSET	FUNDUS APPEARANCE	ELECTRO-OCULOGRAM
Present study	Dominant	4th decade	Variable atrophy and metaplasia of retinal pigment epithelium, drusen occasionally present, subretinal hemorrhages not present	Abnormal
Sorsby's pseudoinflammatory dystrophy ¹⁻⁴ (hereditary hemorrhagic dystrophy ⁶)	Dominant	4th and 5th decades	Early subretinal hemorrhage; fine, diffuse drusen-like deposits reported; peripheral atrophy	Normal
Recessively inherited pseudoinflammatory dystrophy ⁸	Recessive	2nd and 3rd decades	Central and peripheral retinal pigment epithelial atrophy, hypertrophy, and metaplasia; peripheral albinotic changes; fine, intraretinal hyaline deposits	Abnormal in 5 of 10 eyes tested
North Carolina dystrophy ^{9,10}	Dominant	1st decade	Drusen or focal retinal pigment epithelial atrophy, peripheral drusen, and late coloboma-like atrophy of pigment epithelium and choroid	Almost always normal
Age-related macular degeneration	Multifactorial, genetic and non- genetic influences	6th decade	Occasional pseudoinflammatory appearance, drusen always present	

there was no electro-oculographic light rise, although the electroretinogram was only moderately abnormal. In Patient IV-6, the electro-oculogram was severely abnormal. These findings suggest that the choroid or the pigment epithelium was the primary site of disease, with photoreceptors affected secondarily.

The clinical features in this new condition include a dominant inheritance pattern with incomplete penetrance of the gene or possible variable expressivity (since the mother of Patient 2 had no symptoms, yet she transmitted the gene to her offspring). Variable expressivity was documented, in that severe central visual loss did not occur uniformly in family members: Patient 1 (IV-5) had a visual acuity of 20/20, whereas Patient 2 (III-9) and Patient III-24 were legally blind. Visual loss did progress with age, although at least two affected family members were still able to read large-print material in their 70s.

The typical fundus findings in the present dystrophy were atrophy, hyperplasia, and metaplasia of the retinal pigment epithelium suggesting an inflammatory process, but without vitreous cells or degenerative vitreous collapse. Eyes were symmetrically affected. Two family members had drusen, and broad areas of pigment epithelial atrophy were document-

ed in three patients. The degree of pigment epithelial metaplasia was variable, being pronounced in the propositus and less pronounced in his mother and Patient IV-6. Placoid amorphous yellow deposits were identified in one patient and resembled those in an early report of such deposits in pseudoinflammatory dystrophy.⁵ The fundus photographs in the present study document the spectrum of disease that occurs in this condition.

In this study, fluorescein angiographic, electrophysiologic, and histopathologic evidence confirmed that this dystrophy was distinct from age-related macular degeneration, even though some members of the pedigree did have drusen. The present dystrophy also seems distinct from previously described pseudoinflammatory dystrophies, which can be differentiated by mode of inheritance, fundus appearance, and electrophysiologic studies.

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OPHTHALMIC MINIATURE

And are those follies going?
And is my proud heart growing
Too cold or wise
For brilliant eyes
Again to set it glowing?
No, vain, alas! th' endeavor
From bonds so sweet to sever;
Poor Wisdom's chance
Against a glance
Is now as weak as ever.

Thomas Moore, "The Time I've Lost in Wooing," 1834

Long-Term Betaxolol Therapy in Glaucoma Patients With Pulmonary Disease

Robert N. Weinreb, M.D., E. Michael van Buskirk, M.D., Reuben Cherniack, M.D., and Margaret M. Drake, B.A.

We evaluated the use of topically administered betaxolol 0.5% in 101 glaucoma patients (47 men and 54 women) who had chronic obstructive pulmonary disease, asthma, or timolol-induced bronchoconstriction. Betaxolol 0.5% was administered twice daily and patients were reexamined at three-month intervals for up to two years. In addition to measurement of intraocular pressure, pulmonary function tests were obtained before therapy (baseline), two or three weeks after initiating betaxolol therapy, and at yearly intervals. Before treatment with betaxolol, the mean ratio of forced expiratory volumes in one second (FEV₁) to forced vital capacity (FVC) was 66.3% (n = 101). After two weeks of betaxolol treatment, mean FEV₁/FVC ratio was 66.2% (n = 101). After one year of betaxolol therapy, mean FEV_1/FVC ratio was 60.1% (n = 24), and after two years it was 54.4% (n = 5). Nine patients developed symptoms that may have been associated with betaxolol treatment and were withdrawn from the study. Five of these patients developed symptomatic pulmonary obstruction between one and 554 days after initiating betaxolol treatment. Topically administered betaxolol was well tolerated by most glaucoma patients with concomitant pulmonary disease.

IN SUSCEPTIBLE PATIENTS, bronchoconstriction may result from the administration of systemic or topical beta-adrenergic blocking agents. Let a Buskirk and associates reported previously that topical administration of betaxolol, a cardioselective beta-blocking agent, for two to three weeks in 11 glaucoma patients with compromised pulmonary function was not associated with respiratory complications. In the present study, we report the results of administration of betaxolol to 101 glaucoma patients with reduced pulmonary function, 24 of whom were treated for at least one year.

Subjects and Methods

After giving informed consent, 101 patients were enrolled in a multicenter study. All subjects had glaucoma with a concurrent clinical diagnosis of chronic obstructive pulmonary disease (n = 45), asthma (n = 47), or a history of timolol-induced bronchoconstriction (n = 9). Fifty-six patients were taking one or more bronchostimulants for their pulmonary condition at the time of their enrollment. Patients were excluded if they had a history of ocular infection or inflammatory disease, intraocular surgery, ocular trauma, abnormalities preventing reliable applanation tonometry, retinal detachment, diabetic retinopathy or any progressive retinal disease, cardiovascular disease, or other systemic disease in which beta-blocker therapy was contraindicated. Subjects with severe obstructive airway disease, defined as the ratio of forced expiratory volume in one second to forced vital capacity (FEV₁/FVC) of less than 60% of predicted values for the sex, age, and height of the patient, were also excluded.

The original objective of this study was to provide betaxolol on a compassionate use basis to patients with progressive glaucomatous

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damage and pulmonary disease who were receiving maximal intraocular pressure-reducing medications, not including a beta-adrenergic blocking agent. At the time the study was initiated in January 1984, it was judged that timolol, a nonselective beta-blocking agent, could not be tolerated by these patients because of their pulmonary condition. After a number of these patients were enrolled, approval to market ophthalmic betaxolol was obtained and enrollment in this study was increased. The approval of the Human Subjects Committee was obtained at each trial center and informed consent was obtained for each subject before entering the study.

After enrollment, topical administration of any beta-adrenergic blocking agent was discontinued for two weeks, after which baseline spirometry was assessed. Forced vital capacity (FVC) and forced expiratory volume in one second (FEV₁) were measured for each patient and the ratio of FEV₁/FVC was calculated.

Patients were given betaxolol 0.5% ophthalmic solution and instructed to administer it twice daily to each affected eye. If the patient had not previously received ocular beta-blocker therapy, or if there was a history of a pulmonary reaction to timolol, the ophthalmologist administered the first dose and observed the patient for up to four hours. Patients were reexamined after two to three weeks of betaxolol therapy and spirometry was reassessed. Thereafter, spirometry was assessed at yearly intervals. The FEV₁, FVC, and FEV₁/FVC ratio at each time interval were compared with baseline values using a paired t-test. P < .05 was considered significant.

Results

Forty-seven men and 54 women, aged 65 ± 12.42 years (mean ± S.D.), were enrolled. Ninety-one patients were white, eight black, and two Hispanic. Primary open-angle glaucoma was the most common ocular diagnosis (Table 1). More than half of the subjects (85) used at least one intraocular pressure reducing medication upon entry into the study (Table 2).

Pulmonary function tests obtained before administration of betaxolol were compared to those obtained after two weeks of treatment in 101 patients (Table 3). After two weeks, the mean FEV₁, FVC, and FEV₁/FVC ratio were not

TABLE 1
OCULAR DIAGNOSIS

DIAGNOSIS	NO.
Primary open-angle glaucoma	84
Glaucoma suspect	6
Pseudoexfoliative glaucoma	4
Secondary glaucoma	4
Low-tension glaucoma	2
Glaucoma, combined mechanism	1

significantly different from baseline. Pulmonary function tests were also obtained in 24 of these patients one year after betaxolol treatment (Fig. 1). Again, the mean FEV_1 , FVC, and FEV_1/FVC ratio after one year were not significantly different from the values for the same group at baseline. In five patients, pulmonary function tests were obtained after two years of betaxolol therapy (Fig. 2). In these patients, the mean FEV_1 , FVC, and FEV_1/FVC ratio had fallen over the two years but were not statistically different from baseline.

Baseline intraocular pressure was 23 ± 6 mm Hg (mean \pm S.D.). After two weeks, intraocular pressure was 20 ± 5 mm Hg. In the 24 patients whose spirometry values were compared at baseline and one year, baseline intraocular pressure was 23 ± 5 mm Hg. At one year, mean intraocular pressure in this subgroup was 20 ± 3 mm Hg. The subgroup of five patients who participated for two years had a baseline intraocular pressure of 24 ± 8 mm Hg and an intraocular pressure of 21 ± 4 mm Hg after two years of betaxolol therapy. In these patients, there was a 13% reduction of intraocular pressure from baseline at each subsequent time interval.

Seventy-one of the subjects (70%) continue to

NUMBER OF INTRAOCULAR PRESSURE
REDUCING MEDICATIONS USED BEFORE
STUDY ENTRY

NO. OF MEDICATIONS	NO. OF PATIENTS
None	16
1	49
2	25
3 or more	11

TABLE 3
PULMONARY FUNCTION VALUES AT BASELINE AND AFTER TWO WEEKS OF BETAXOLOL THERAPY (MEAN \pm S.D.)

	NO.	FEV ₁ (L)	FVC (L)	FEV ₁ /FVC (%)	
Baseline	101	1.79 ± 0.86	2.63 ± 0.98	66.3 ± 14.48	
Two wks	101	1.81 ± 0.82	2.69 ± 0.96	66.2 ± 17.48	

administer betaxolol, and 30 (30%) have discontinued for several reasons. Treatment was considered a failure in five subjects because intraocular pressure was not reduced sufficiently. One subject was subsequently excluded because preexisting age-related macular degeneration was a criterion for exclusion from enrollment. Fifteen patients discontinued betaxolol for reasons unrelated to therapy. Finally, treatment was discontinued in nine subjects because of adverse medical events (Table 4).

Subject 1 developed recurrent vertigo and unsteadiness five months after initiating betaxolol therapy. Symptoms disappeared within two weeks of discontinuation of therapy.

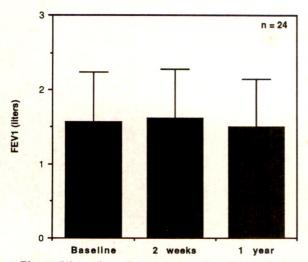
Eighteen months after initiating betaxolol treatment, Subject 2, who had a history of frequent hospitalization for asthma before initiating betaxolol therapy, was hospitalized for an asthmatic attack. Her condition improved with administration of prednisone and bronchodilators; betaxolol therapy continued at this time. After another asthmatic attack which required

hospitalization, betaxolol therapy was discontinued. The patient was hospitalized again one month later, even though betaxolol had not been administered during this time. The pulmonologist who treated this patient attributed her frequent attacks to seasonal allergy.

Upon enrollment into the study, an ophthal-mologist discontinued theophylline in a third patient (Subject 3) with chronic obstructive pulmonary disease. Five days after initiating betaxolol therapy, the patient called to complain of shortness of breath. The patient discontinued betaxolol treatment and her condition improved. The FEV₁/FVC ratio at baseline was 74%, and six days later while on betaxolol it was 75%. Although there was no difference in the FEV₁/FVC ratio during this time, treatment with theophylline was reinstituted and the patient chose to withdraw from the study. Subsequently, the patient refused to have pulmonary function testing after rechallenge with betaxolol.

Another patient (Subject 4) with chronic emphysema noticed increased shortness of breath 24 hours after starting the study. The patient continued to administer betaxolol for two weeks, after which time another ocular antihypertensive medication was substituted and the patient was withdrawn from the study. The FEV₁/FVC ratio was 54% at baseline and 41% after two weeks on betaxolol therapy. This patient refused to undergo a rechallenge.

Subject 5, who had a myocardial infarction 18 months before entry into the study, died from a



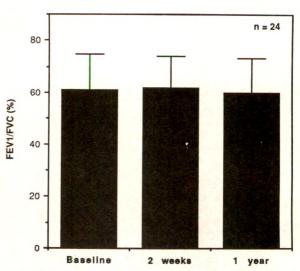


Fig. 1 (Weinreb and associates). The mean FEV_1 (left) and FEV_1/FVC ratio (right) after one year of betaxolol treatment were not significantly different from the values for the same group at baseline.

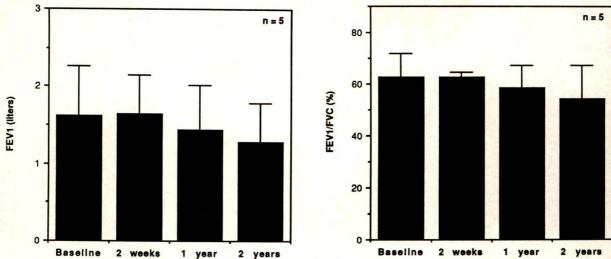


Fig. 2 (Weinreb and associates). The mean FEV₁ (left) and FEV₁/FVC ratio (right) after two years of betaxolol treatment were not significantly different from the values for the same group at either baseline or one year.

myocardial infarction three months after initiating betaxolol therapy. It was doubtful that betaxolol was a contributing factor in this patient's death.

Subject 6 was a 68-year-old man with moderate obstructive airway disease who had an asymptomatic decrease in FVC (600 cc) and FEV₁ (400 cc) after two weeks on a regimen of betaxolol, although the FEV₁/FVC ratio did not change significantly. During this time, he had an episode of shortness of breath with exertion and thickened bronchial secretions. The FEV₁/FVC ratio was 57% at baseline, 53% at two weeks, and 51% after four weeks of betaxolol treatment. After discontinuing betaxolol, the patient refused to have pulmonary function

testing after rechallenge to evaluate further the effects of betaxolol.

Subject 7 was a 71-year-old woman with a ten-year history of hyperthyroidism without any history of cardiac problems. Six months after entering the study, she had an electrocardiogram that showed a new bundle branch block. Betaxolol treatment was discontinued. Attempts by an ophthalmologist to follow up on the cause and possible role of betaxolol in the development of the defect were unsuccessful and the subject was withdrawn from the study.

Subject 8, a 76-year-old woman with a 15-year history of rheumatoid arthritis and bronchial asthma, experienced cardiac arrhythmia and

TABLE 4
ADVERSE EFFECTS OCCURRING DURING STUDY

SUBJECT NO.	ADVERSE EFFECT	COMMENT	NO. OF DAYS ON BETAXOLOL
1	Vertigo, dizziness	<u> </u>	28
2	Hospitalized for asthma	Seasonal allergy	554
3	Dyspnea	Occurred after discontinuing theophylline therapy	5
4	Shortness of breath, wheezing	_	1
5	Deceased	Myocardial infarction	113
6	Symptomatic bronchial congestion	Not corroborated by pulmonary function test results	170
7	Bundle branch block	Hyperthyroid	176
8	Cardiac arrhythmia and shortness of breath		455
9	Syncope	Associated with nitroglycerin and prolonged standing	84

shortness of breath after having administered betaxolol for over one year. Her internist recommended that she be withdrawn from participating in the study.

Three months after entering the study, Subject 9, a 70-year-old man with hypertension and diabetes mellitus, had an episode of weakness with substernal pressure after his routine two-mile run. Nitroglycerin was prescribed as necessary. While standing in a hot, crowded church the following Sunday, he had a synco-pal episode after administering a nitroglycerin tablet. His cardiologist recommended that he be withdrawn from beta-adrenergic blocking therapy.

Discussion

The incidence of patients who have both asthma or chronic obstructive lung disease and glaucoma is unknown. Lorber, Kaltenborn, and Burrows⁶ demonstrated that 20% of a random population of normal subjects had significant bronchial reactivity to an inhaled bronchodilator. This may approximate the incidence of sensitivity to a bronchoconstricting stimulant such as a beta-adrenergic blocking agent. Bronchial responsiveness may also be influenced by exercise⁷ and environmental elements such as humidity, air temperature,8 allergies,9 or respiratory infections. 10 The observation that chronic obstructive pulmonary disease may be more common in the elderly is particularly relevant, since glaucoma is frequently diagnosed and treated in an aged population.

Several clinical studies have suggested a greater safety potential for topical administration of betaxolol, a cardioselective betablocking agent, to glaucoma patients with coexisting pulmonary disease as compared with the nonselective beta-blocking agent, timolol.2,4,5 Schoene and associates and Dunn and associates2 reported that betaxolol 1% did not significantly decrease airflow in contrast to the significant reduction caused by timolol 0.5%. It has also been demonstrated that the changes in ventilatory function after administration of timolol were related to the degree of airway hyperresponsiveness present.2 Van Buskirk and colleagues4 compared pretherapy baseline pulmonary function tests to results obtained after two weeks of betaxolol therapy in 11 glaucoma subjects. The preliminary data in this small group of patients suggested that betaxolol might be useful for treating many glaucoma patients with compromised pulmonary function.

In this study, we compared pulmonary function tests obtained at baseline and two weeks after betaxolol treatment in 101 subjects, after one year of treatment in 24 subjects, and two years after treatment in five subjects. The mean FEV₁/FVC values for 101 subjects showed no change over two weeks. Additionally, no significant change was noted in the mean FEV₁/FVC values for 24 subjects after one year of therapy or for five subjects after two years of therapy. After two years, however, mean FEV₁ had decreased by 330 cc. The decrease in FEV₁ of 165 cc per year is greater than the mean rate of decline in healthy subjects, but consistent with the changes seen in chronic obstructive pulmonary disease. 11 Hence, we observed little change in FEV₁/FVC values over time, despite the relative severity of pulmonary conditions in some of these patients and the variable nature of their disease (upon study entry, 45 subjects were taking one or more prescription medications for their pulmonary disease and 15 were taking three or more medications to control bronchial reactivity). Although precipitating factors of an asthmatic episode are difficult to determine, only five of the subjects followed up two weeks or longer discontinued use of betaxolol because of exacerbation of their pulmonary function.

Our findings support previous conclusions⁴ that betaxolol is useful for treating many glaucoma patients with compromised pulmonary function. Because of the potential of these betaadrenergic blocking agents to exacerbate preexisting pulmonary disease, ophthalmologists need to obtain a thorough medical history initially and monitor respiratory symptoms during the course of treatment. Not all glaucoma patients with pulmonary disease can tolerate betaxolol. In certain cases, laboratory investigations such as baseline and posttreatment pulmonary function studies can assist in the identification of patients for whom a cardioselective beta-adrenergic blocking agent may be most appropriate.

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OPHTHALMIC MINIATURE

But though the picture weary out the eye, By nature an unmanageable sight, It is not wholly so to him who looks In steadiness, who hath among least things An under-sense of greatest; sees the parts As parts, but with a feeling of the whole.

William Wordsworth, "The Prelude. Book Seventh," 1798-1839

Comparative Efficacy of the \(\beta \)-Blockers for the Prevention of Increased Intraocular Pressure After Cataract Extraction

David R. West, M.D., Timothy D. Lischwe, M.D., Vance M. Thompson, M.D., and Carl H. Ide, M.D.

We conducted a randomized, doublemasked study of intraocular pressure in 80 patients treated with betaxolol, levobunolol, timolol, or placebo after extracapsular cataract extraction. Intraocular pressures were measured preoperatively and early (four to seven hours) and late (20 to 24 hours) postoperatively. There was a significant mean increase in pressure from the preoperative period to the early postoperative period for the placebo group (5.35 mm Hg), betaxolol group (6.73 mm Hg), and the timolol group (3.83 mm Hg). However, the levobunolol group had a mean decrease in pressure (0.43 mm Hg). There was no significant difference between preoperative and late postoperative pressures for any of the groups. One-way analysis of covariance of the changes in pressure from the preoperative to early postoperative period showed a significant increase for the placebo and betaxolol groups compared to the levobunolol group, without significant difference between the levobunolol and timolol groups. Overall, levobunolol proved most effective in preventing an increase in intraocular pressure after extracapsular cataract extraction; timolol was partially effective.

INTRAOCULAR PRESSURE increase after intracapsular¹⁻⁵ and extracapsular⁶ cataract extraction has been described previously. The pressure rise was more prolonged and more pronounced in patients with preexisting glau-

coma. 7,8 The use of alpha-chymotrypsin 1,2 or sodium hyaluronate^{9,10} accentuated the pressure rise, whereas acetylcholine11 and carbachol12 blunted the pressure rise after cataract extraction. After intracapsular cataract extracwithout alpha-chymotrypsin, Radtke, and Cohan³ found an average peak pressure of 39.0 mm Hg (range, 26 to 50 mm Hg) at 6.8 hours.

The rise in intraocular pressure after cataract extraction has been prevented or reduced by many agents used for glaucoma. Acetazolamide13 and timolol13-15 have decreased the pressure rise 24 hours after intracapsular extraction. Haimann and Phelps16 also demonstrated the effectiveness of timolol six hours after intracapsular surgery. However, after extracapsular extraction, timolol showed minimal effect on the postoperative pressure rise 24 hours after surgery. 17,18

We conducted a randomized, double-masked study to compare the efficacy of the β-blockers (betaxolol, timolol, and levobunolol) on the early postoperative rise in intraocular pressure after extracapsular cataract extraction and posterior chamber lens placement with the use of sodium hyaluronate and acetylcholine.

Patients and Methods

Eighty patients scheduled for extracapsular cataract extraction and posterior chamber lens placement with the use of sodium hyaluronate and acetylcholine were randomly assigned to one of four treatment groups. Each of the following groups had 20 participants: Group 1, betaxolol; Group 2, 0.5% timolol; Group 3, levobunolol; and Group 4, placebo (artificial tears). All patients were men with a mean age (range) of 67 years (51 to 84 years) in Group 1; 70 years (58 to 96 years) in Group 2; 71 years (59 to 91 years) in Group 3; and 69 years (54 to 81 years) in Group 4. Each patient received two

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drops of their assigned treatment immediately before patching the eye after surgery. The operations were performed by one of three of us (D.R.W., T.D.L., or C.H.I.). Patients were excluded if they had previous ocular surgery, uveitis, glaucoma, preoperative intraocular pressure above 22 mm Hg, or a chronic need for ocular medication.

All intraocular pressures were measured with the same Goldmann applanation tonometer. Pressures were taken preoperatively and postoperatively at four to seven hours and again at 20 to 24 hours. The three pressure measurements on each patient were taken by the same examiner. Measurements were made with the tonometer prism aligned vertically and horizontally to correct for astigmatism, and the mean value was determined.

Pupils were dilated preoperatively, with three sets of one drop each of 2.5% phenylephrine, 1% tropicamide, and 1% cyclopentolate approximately five minutes apart. Each patient was given an O'Brien or a Van Lint facial nerve block (5.0 \pm 1.0 ml), or both, and a retrobulbar block with a mixture of 2% lidocaine with epinephrine and 0.75% bupivacaine (3.5 ± 0.5) ml). Digital pressure was applied preoperatively after the retrobulbar block was given until intraocular pressure by Schiøtz tonometer was less than 10 mm Hg. All patients received epinephrine (1.0 ml of 1:1,000 dilution added to 500 ml of BSS) during irrigation to enhance pupillary dilation. Sodium hyaluronate was injected intracamerally before placement of a 6.0-mm posterior chamber lens. The sodium hyaluronate was then aspirated from the anterior chamber. Acetylcholine 1% solution (0.5 ± 0.25 ml) was then injected into the anterior chamber to induce miosis. The surgical wound was closed watertight with seven to ten 10-0 interrupted nylon sutures. Gentamicin (0.5 ml) and betamethasone (0.5 ml) were given at the end of surgery subconjunctivally.

One-way analysis of covariance, a test that statistically adjusts for baseline differences between groups, was computed on the mean intraocular pressure data gathered at the preoperative and early and late postoperative time periods.

Results

A significant mean increase in intraocular pressure from the preoperative to the early

(four to seven hours) postoperative period was noted in the betaxolol-treated group (6.73 mm Hg, P = .0002), the placebo-treated group (5.35 mm Hg, P = .0037), and the timolol-treated group (3.83 mm Hg, P = .039). However, the levobunolol-treated eyes showed a mean decrease in pressure of 0.43 mm Hg in the early preoperative period (Fig. 1).

One-way analysis of covariance of the change in pressure from the preoperative to the early postoperative periods demonstrated a significant increase in betaxolol-treated eyes compared to levobunolol-treated eyes (P = .0032). The placebo-treated eyes had a significant pressure rise compared to levobunolol-treated eyes (P = .0203). The timolol- and betaxolol-treated groups were not statistically different from one another or from the placebo-treated group. Although there was a strong tendency for levobunolol to control the early postoperative pressure rise compared to timolol, the difference was not statistically significant (P = .087).

The mean preoperative pressures were 14.4 mm Hg in the betaxolol group, 13.8 mm Hg in the placebo group, 13.7 mm Hg in the timolol group, and 13.5 mm Hg in the levobunolol group (Table 1). These pressures did not differ significantly among the four groups (Fig. 2). No significant changes in intraocular pressure from the preoperative measurements were

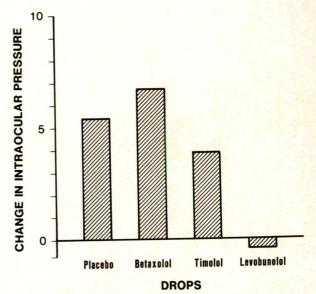


Fig. 1 (West and associates). Comparison of the mean change in intraocular pressure from the preoperative to early postoperative time periods for each treatment group.

TABLE 1
INTRAOCULAR PRESSURE VALUES
(MM Hg)

		TIME			
TREATMENT		POSTOPERATIVE PERIOD			
GROUP	PREOPERATIVE	EARLY	LATE		
Placebo					
Mean ± S.D.	13.8 ± 3.3	19.1 ± 9.0	14.3 ± 5.0		
Range	(8–19)	(4-41)	(5-28.5)		
Betaxolol					
Mean ± S.D.	14.4 ± 3.8	21.1 ± 9.7	15.7 ± 5.4		
Range	(5.5-21.5)	(5-45)	(7-28)		
Timolol					
Mean ± S.D.	13.7 ± 3.0	17.5 ± 7.4	14.9 ± 5.0		
Range	(7–19)	(9-28.5)	(8.5-26.5)		
Levobunolol					
Mean ± S.D.	13.5 ± 4.0	13.1 ± 5.1	14.0 ± 6.0		
Range	(8-22)	(5-25)	(5-35)		

noted at 24 hours in any of the four treatment groups.

During the early postoperative period, six placebo-treated eyes (30%), eight betaxolol-treated eyes (40%), six timolol-treated eyes (30%), and one levobunolol-treated eye (5%)

TABLE 2
PATIENTS WITH INCREASED INTRAOCULAR
PRESSURE

PRI			PRE	INTRAOCULAR PRESSURE ≥ 30 MM Hg					
POS	TOPERA	TIVE P	ERIOD	POS		OPERATIVE PERIOD			
EARLY		L	ATE	EARLY LATE			TE		
NO.	(%)	NO.	(%)	NO.	(%)	NO.	(%)		
6	(30)	1	(5)	3	(15)	0	(0)		
8	(40)	2	(10)	4	(20)	0	(0)		
6	(30)	2	(10)	1	(5)	0	(0)		
1	(5)	1	(5)	0	(0)	1	(5)		
	POS EA NO. 6 8 6	PRESSURE POSTOPERA EARLY NO. (%) 6 (30) 8 (40) 6 (30)	PRESSURE ≥ 23 M POSTOPERATIVE P EARLY L NO. (%) NO. 6 (30) 1 8 (40) 2 6 (30) 2	NO. (%) NO. (%) 6 (30) 1 (5) 8 (40) 2 (10) 6 (30) 2 (10)	PRESSURE ≥ 23 MM HG PRE POSTOPERATIVE PERIOD EARLY LATE E/ NO. (%) NO. (%) NO. 6 (30) 1 (5) 3 8 (40) 2 (10) 4 6 (30) 2 (10) 1	PRESSURE ≥ 23 MM HG PRESSURE POSTOPERATIVE PERIOD PER EARLY LATE EARLY NO. (%) NO. (%) NO. (%) 6 (30) 1 (5) 3 (15) 8 (40) 2 (10) 4 (20) 6 (30) 2 (10) 1 (5)	PRESSURE ≥ 23 MM Hg PRESSURE ≥ 30 MM POSTOPERATIVE PERIOD PERIOD EARLY LATE EARLY LA NO. (%) NO. (%) NO. (%) NO. (%) NO. 6 (30) 1 (5) 3 (15) 0 8 (40) 2 (10) 4 (20) 0 6 (30) 2 (10) 1 (5) 0		

had intraocular pressures of 23 mm Hg or greater (Table 2). An intraocular pressure of 30 mm Hg or greater at four to seven hours after surgery was found in three placebo-treated (15%), four betaxolol-treated (20%), one timolol-treated (5%), and none of the levobunolol-treated eyes (Table 2). During the early postoperative period, five placebo-treated eyes (25%), six betaxolol-treated eyes (30%), five timolol-treated eyes (25%), and one levobunolol-treated eye (5%) experienced a pressure rise of 10 mm Hg or greater.

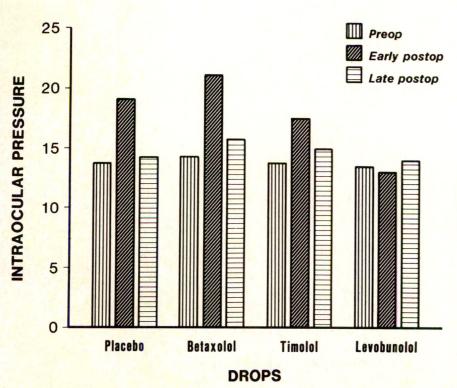


Fig. 2 (West and associates). Comparison of the mean intraocular pressures preoperatively and early and late postoperatively for each treatment group.

Postoperatively, there was no marked difference in the amount of cell and flare noted between the four treatment groups. None of the patients in the study experienced any systemic or ocular side effects from the agents used. No postoperative hyphemas or wound leaks were noted in any of the patients.

Discussion

In the late 1960s, topical propranolol was the first adrenergic β-blocking agent used to lower intraocular pressure.19 Since that time, many other \u03b3-blocking agents have been evaluated for their effectiveness in lowering intraocular pressure. Their mechanism of action appears to be a decrease in aqueous humor formation in the treated eye. Coakes and Brubaker20 demonstrated a 34% mean decrease in aqueous humor production in eyes treated with timolol. The onset of action of the topical β-blockers occurs within one hour after instillation and lasts approximately 24 hours.21

Timolol and levobunolol affect the β_1 and β_2 receptors and, thus, are nonselective. Betaxolol, however, is a β-selective agent affecting only β₁ receptor sites. Animal experiments have demonstrated the probability that the β2 receptor is predominant in affecting intraocular pressure.22,23 If so, then it is uncertain how betaxolol works if receptors in the eyes are of the β2 subtype. Chiou and associates24 suggested that the β-blockers might actually work via dopamine antagonism rather than their adrenergic effect. Others have suggested that betaxolol may reach high enough concentrations in the aqueous humor to overcome its β₁ selectivity and block the β2 receptors. 25 In our study, betaxolol showed no effect on diminishing the early rise of pressure seen after extracapsular surgery. Perhaps betaxolol does not reach the concentration needed to block the β2 receptors in the early postoperative period after a single dose (two drops).

Levobunolol and timolol are both nonselective agents, but levobunolol showed a greater ability to control early postoperative pressure rises. Eyes treated prophylactically with levobunolol had a lower incidence of pressure rises greater than 10 mm Hg from baseline than those treated with timolol (5% vs 25%). Levobunolol is metabolized into dihydrolevobunolol, which is an equally active and potent agent. Timolol does not appear to have an active breakdown product. The presence of this active metabolite may explain levobunolol's effectiveness compared to timolol in the early postoperative period when the eye is in a hypermetabolic state.

The cause of the increased intraocular pressure seen after cataract extraction is probably multifactorial in nature. Decreased outflow facility appears to play a major role. Rothkoff, Biedner, and Blumenthal²⁶ found increased intraocular pressure (>24 mm Hg) in 14 of 60 patients (23%) who had intracapsular cataract extraction through a limbal incision vs none of 35 patients who had a corneal cataract incision, implying that damage to the trabecular meshwork accounted for the decreased outflow facility. Other studies have implicated permeability changes in the blood-aqueous barrier caused by postoperative inflammation and increased protein in the aqueous humor.27,28 Tight wound closure also plays a role in increased postoperative intraocular pressure. Galin, Lin, and Obstbaum5 showed a significant positive correlation between the number of sutures placed and the rise in pressure at 24 hours. The corneoscleral sutures themselves may contribute to increased pressure by distorting the angle or by increasing inflammation or localized corneal edema.

The use of sodium hyaluronate during cataract surgery has been associated with increased postoperative intraocular pressure. The pressure rise peaks at two hours after injection and returns to normal levels within eight to 24 hours.29 Pressure increases were found to be significantly lower and less prolonged with anterior chamber washout of the sodium hyaluronate as opposed to leaving the sodium hyal-

uronate in the eye.9

Sharp increases in intraocular pressure can be detrimental to susceptible eyes. Hayreh³⁰ reported 13 cases of anterior ischemic optic neuropathy following cataract surgery. Eleven of these patients had documented postoperative pressure increases. Patients with a history of postcataract anterior ischemic optic neuropathy also have a high risk of developing it in the second eye. Patients with preexisting glaucoma are also susceptible to a short-term pressure rise after cataract extraction. Savage and associates⁷ found that 9.7% of glaucomatous eyes with severe preoperative field loss (split fixation or central field ≤10 degrees) had additional field loss after extracapsular cataract extraction. McGuigan and coworkers8 found a pressure rise of 7 mm Hg or greater in 62% of glaucomatous eyes compared to 10% of control

eyes 24 hours after extracapsular cataract extraction.

Various antiglaucomatous medications are used to control pressure rises after cataract surgery. Acetazolamide given prophylactically has decreased the pressure rise at 24 hours after intracapsular extraction.27 Pilocarpine gel has been shown to reduce the 24-hour postoperative intraocular pressure from a mean of 28.1 mm Hg in controls to 19.4 mm Hg in treated eyes. 18 Timolol has been effective at six16 and 2413-15 hours after intracapsular procedures, but has minimal effect at 24 hours after extracapsular surgery with 18 or without 17 the use of sodium hyaluronate. Levobunolol has recently been shown to reduce the rise in pressure after extracapsular surgery at 24 hours. Our study was conducted to determine the effectiveness of the β-blockers during the early postoperative period, at the peak pressure rise a few hours after surgery. Further studies are needed to compare the effectiveness of levobunolol, pilocarpine gel, and acetazolamide in controlling postoperative pressure rises.

The results of our study concurred with previous results showing a significant rise in intraocular pressure in the early postoperative period (four to seven hours) after cataract extraction. Betaxolol had no effect on this pressure rise, whereas timolol appeared only to be partially effective. Levobunolol demonstrated marked effectiveness in blunting this early rise in pressure.

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Oculab Tono-Pen, Goldmann Applanation Tonometry, and Pneumatic Tonometry for Intraocular Pressure Assessment in Gas-Filled Eyes

Michael W. Hines, M.D., Bradley F. Jost, M.D., and Karen L. Fogelman, R.N.

We performed 84 intraocular pressure measurements with the Oculab Tono-Pen, Goldmann applanation tonometer, and pneumatic tonometer in 47 eyes that had undergone pars plana vitrectomy and gas-fluid exchange. Measurements made by using the Tono-Pen were accurate when compared to those made by Goldmann tonometry (mean difference, 0.74 mm Hg). In a subset of eyes with increased intraocular pressure (≥25 mm Hg), the Tono-Pen provided measurements similar to those made by Goldmann applanation tonometry (P > .60), with only three of 39 readings (8%) underestimating the Goldmann pressure by more than 3 mm Hg. Pneumatic tonometry significantly underestimated the intraocular pressure in eyes with increased pressure (P < .001), with 20 of 39 readings (51%) underestimating the Goldmann pressure by 5 mm Hg or more.

RECENT EVALUATIONS of the Oculab Tono-Pen have suggested that it is a clinically accurate instrument for measuring intraocular pressure. 1-3 The Tono-Pen is a streamlined, handheld instrument that does not require a slit lamp or other accessory instruments. The operating principle of the Tono-Pen is similar to that of the Mackay-Marg tonometer. The Tono-Pen uses a strain gauge that converts intraocular pressure into an electrical signal. As the tip touches the cornea, the gauge is activated and increasing force is applied until the cornea is flattened by the foot plate. When this occurs, the foot plate itself relieves some of the force,

causing a dip in the force curve. The built-in single chip microprocessor of the Tono-Pen senses this change and accepts the reading as valid. Several readings are averaged automatically to provide a final digital reading along with the range of the coefficient of variance (5%, 10%, 20%, >20%).

These previous studies, however, have not assessed the Tono-Pen's accuracy in measuring intraocular pressure in eyes that are gas-filled following vitreous surgery. In these eyes, the method of assessment of intraocular pressure is critical to obtaining an accurate measurement. Intraocular gases are readily compressed by tonometric methods that involve indentation (Schiøtz tonometry and pneumatic tonometry), leading to an underestimation of intraocular pressure. Experimental data have shown applanation tonometry to be more accurate than either Schiøtz tonometry or pneumatic tonometry in estimating the actual intraocular pressure in gas-filled eyes.⁴

We designed this study to compare the Tono-Pen to Goldmann applanation tonometry in the measurement of intraocular pressure in gasfilled eyes. Additionally, we compared pneumatic tonometry to Goldmann applanation tonometry in such eyes.

Subjects and Methods

We made 96 consecutive assessments of intraocular pressure in 47 patients who had undergone pars plana vitrectomy and gas-fluid exchange. Surgery was performed for proliferative diabetic retinopathy with nonclearing vitreous hemorrhage or traction retinal detachment of the macula (16 cases), proliferative vitreoretinopathy (12 cases), and complex retinal detachments involving vitreous hemorrhage, posterior breaks, giant retinal tears, or

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macular holes (19 cases). Sulfur hexafluoride was used in 23 cases in concentrations between 10% and 30%. Perfluoropropane was used in 21 cases in concentrations varying from 10% to 15%. Three additional cases had gas-fluid exchanges with air. Of the 96 assessments, 47 were performed on the first postoperative day, 29 on the second day, and 20 on the third or later postoperative day.

Intraocular pressure was measured with a production model Oculab Tono-Pen, a Goldmann applanation tonometer attached to a slit lamp, and a pneumatic tonometer. All pressures were measured while the patient was seated. The eyes were numbered consecutively, and in eyes with odd numbers the Tono-Pen measurement was performed first followed by Goldmann applanation; in eyes with even numbers Goldmann applanation was performed first followed by Tono-Pen measurement. Pneumatic tonometry was performed last in all eyes.

The Tono-Pen measurements were all made by one of us (K.L.F.). The transducer tip was brought into contact with the cornea after a drop of proparacaine hydrochloride 0.5% had been administered. Several reapplanations were performed until the Tono-Pen indicated a successful measurement by a beep. The same procedure was performed a second time and the two readings were averaged. Readings that did not attain a reliability of 5% were rejected and measurements were repeated until two values were obtained with a 5% reliability.

Goldmann tonometry was performed by one of us (M.W.H.) using the following standardized procedure. A small amount of fluorescein was administered to the inferior cul-de-sac with a moistened fluorescein strip. A masked, independent observer adjusted the tonometer to 15 mm Hg. The mires were aligned by the investigator without looking at the gauge and the observer recorded the reading to the nearest millimeter of mercury and reset the gauge to 15 mm Hg. A second measurement was made by using the same technique and the results were averaged. If the readings differed by over 4 mm Hg, the procedure was repeated until two consecutive readings within 4 mm Hg of each other were obtained. The Tono-Pen and Goldmann tonometer readings were performed and the results recorded in a masked fashion.

After the Tono-Pen and Goldmann tonometer readings had been obtained, two consecutive measurements of intraocular pressure were made by pneumatic tonometry and these values were averaged. Both investigators (M.W.H. and K.L.F.) read the digital display from the pneumatic tonometer in an unmasked fashion when a steady display had been attained after four to five seconds of corneal contact.

In 12 of the 96 assessments, we were unable to obtain reliable intraocular pressure measurements with the Goldmann applanation tonometer. These assessments were not included in the final group for analysis. In eight cases, there was sufficient corneal edema with epithelial irregularity to preclude accurate Goldmann applanation tonometry. In three cases, postoperative eyelid swelling and in one case marked nystagmus prevented us from obtaining Goldmann applanation readings.

The remaining 84 sets of intraocular pressure data were analyzed with Student's paired *t*-test. A subset in which the mean Goldmann applanation reading was 25 mm Hg or greater was also analyzed with Student's paired *t*-test.

Results

Analysis of all 84 data points provided a mean (± S.D.) intraocular pressure of 25.99 ± 8.57 mm Hg with the Tono-Pen and 25.25 \pm 8.37 mm Hg with the Goldmann tonometer. This difference was statistically significant (P < .05). However, the subset of 39 readings in which the Goldmann tonometer gave a mean intraocular pressure reading of 25 mm Hg or greater showed no significant difference between Tono-Pen and Goldmann tonometer readings (P > .60). In this smaller group, the mean Tono-Pen pressure was 32.77 ± 6.12 mm Hg and the mean Goldmann tonometer pressure was 32.59 ± 4.83 mm Hg. Figure 1 shows the good correlation between Tono-Pen and Goldmann tonometer readings, which is maintained for Goldmann pressures over 25 mm Hg.

Pneumatic tonometry provided readings that were significantly lower than Goldmann measurements (P < .001) (Fig. 2). When all readings were considered, the difference in the mean was about 3 mm Hg (Goldmann tonometry, 25.25 ± 8.37 mm Hg vs pneumatic tonometry, 22.55 ± 6.45 mm Hg). The difference was even greater for the 39 eyes with Goldmann pressures of 25 mm Hg or greater, with pneumatic tonometry yielding an average of 27.95 ± 3.76 mm Hg compared to a Goldmann reading of 32.59 ± 4.83 mm Hg (Fig. 2)

 32.59 ± 4.83 mm Hg (Fig. 2).

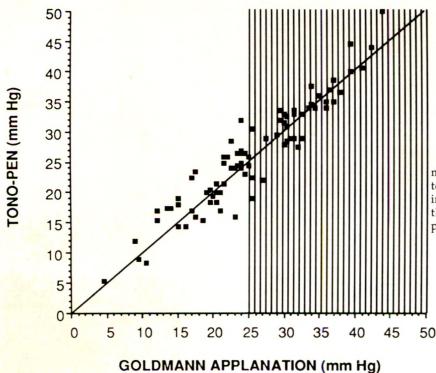


Fig. 1 (Hines, Jost, and Fogelman). Comparison of Goldmann tonometer with the Tono-Pen readings (P < .05). The shaded area to the right represents Goldmann pressures of ≥ 25 mm Hg (P > .60).

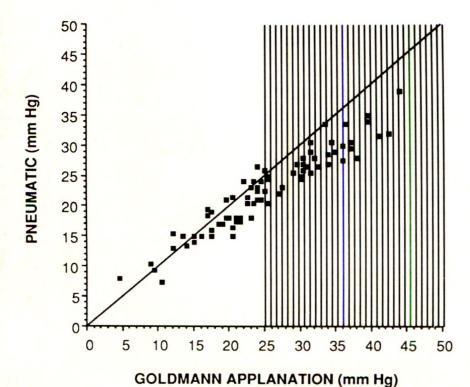


Fig. 2 (Hines, Jost, and Fogelman). Comparison of Goldmann tonometer with the pneumatic tonometer readings (P < .001). The shaded area to the right represents Goldmann pressures of \geq 25 mm Hg (P < .001). Data points below the diagonal line represent underestimation of pressure by the pneumatic tonometer.

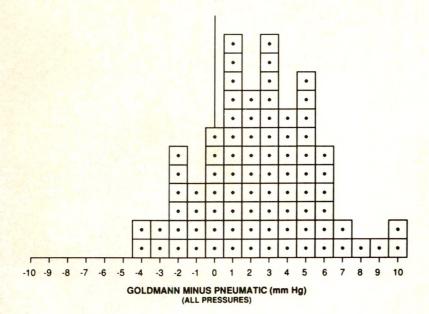


Fig. 3 (Hines, Jost, and Fogelman). Difference between Goldmann tonometer and pneumatic tonometer readings. Points to the left of vertical midline represent overestimation by the pneumatic tonometer. Points to right, underestimation by pneumatic tonometer.

In general, there was a tendency to underestimate intraocular pressure by pneumatic tonometry (Fig. 3) and a slight tendency toward overestimation by the Tono-Pen (Fig. 4) compared to Goldmann tonometry. When Goldmann tonometer readings of 25 mm Hg or

greater were evaluated, this tendency toward underestimation by the pneumatic tonometer was even more exaggerated (Fig. 5). Tono-Pen measurements of these same eyes, however, showed the greater accuracy of the Tono-Pen (Fig. 6). For the Tono-Pen, 31 (79%) measure-

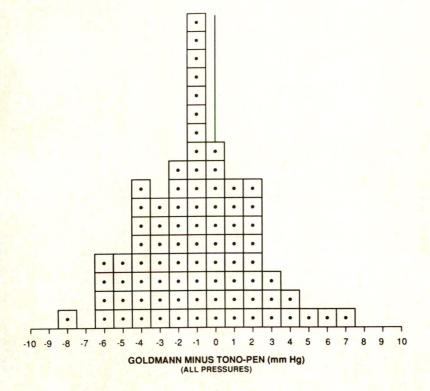


Fig. 4 (Hines, Jost, and Fogelman). Difference between Goldmann tonometer and Tono-Pen readings. Points to the left of vertical midline represent overestimation by Tono-Pen. Points to the right, underestimation by Tono-Pen.

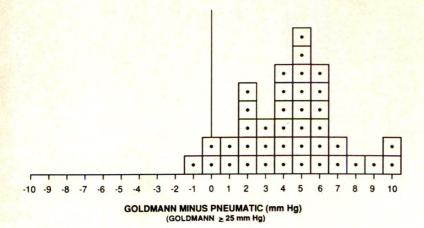


Fig. 5 (Hines, Jost, and Fogelman). Difference between Goldmann tonometer and pneumatic tonometer readings for eyes with a Goldmann pressure of ≥25 mm Hg. Nearly all points lie to the right of the vertical midline and represent underestimations of pressure by the pneumatic tonometer.

ments fell within 3 mm Hg of Goldmann readings, with five (13%) overestimations of the pressure by 4 to 6 mm Hg and three (8%) underestimations of the pressure by 4 to 6 mm Hg. The three cases in which the Tono-Pen underestimated intraocular pressure by more than 3 mm Hg involved eyes with Goldmann readings of 25.5 mm Hg (Tono-Pen, 19 mm Hg), 27 mm Hg (Tono-Pen, 22 mm Hg), and 32 mm (Tono-Pen, 27.5 mm Hg). Visionthreatening increases in intraocular pressure were not read as normal values by the Tono-Pen. In contrast, by pneumatic tonometry there were only 13 readings (33%) within 3 mm Hg of Goldmann measurements, with the remaining 26 (67%) all representing underestimations of greater than 3 mm Hg. Of the pneumatic tonometer readings, 20 (51%) were 5 mm Hg or greater underestimations, with up to 10 mm Hg of underestimation (Fig. 5). The largest under-

estimations by pneumatic tonometry were made in eyes with dangerously increased pressures; by Goldmann tonometry the readings were 42.5, 41, 38, and 36 mm Hg, and by pneumatic tonometry they were 32, 31.5, 28, and 27.5 mm Hg, respectively.

Discussion

We found the Tono-Pen to be satisfactory when compared to Goldmann tonometry in measuring intraocular pressure in gas-filled eyes. Although the Tono-Pen measurements were significantly different from Goldmann tonometry readings, when all levels of intraocular pressure were considered these differences were not deemed to be clinically important for gas-filled eyes in the immediate postoperative

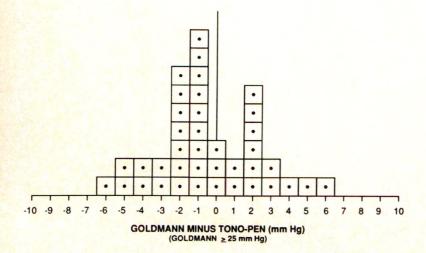


Fig. 6 (Hines, Jost, and Fogelman). Difference between Goldmann tonometer and Tono-Pen readings for eyes with a Goldmann pressure of ≥25 mm Hg. Points to the left of vertical midline represent overestimation of pressure by Tono-Pen; to the right, underestimation.

period. In the more important category of eyes with Goldmann tonometry measurements of 25 mm Hg or greater, we were unable to detect any significant difference between the Tono-Pen and the Goldmann tonometer. In general, the Tono-Pen had a slight tendency to overestimate intraocular pressure in our study (Figs. 3 and 6). No eyes had dangerously increased intraocular pressures that were not detected by the Tono-Pen.

Conversely, the pneumatic tonometer significantly underestimated intraocular pressure in these gas-filled eyes (Figs. 2, 4, and 5). This tendency was greatest in eyes with increased intraocular pressure. Underestimations of up to 10 mm Hg were made by the pneumatic tonometer. Of 39 eyes with Goldmann readings of 25 mm Hg or greater 20 (51%) were underestimated by 5 mm Hg or more. These findings with pneumatic tonometry confirm previous experimental data⁴ and relate to the compressibility of gas and to pneumatic tonometry as an indentation type of tonometry.

Although not a major objective of our study, we found that the Tono-Pen could be used in eyes in which it was not possible to use Gold-

mann applanation tonometry (eyes with marked eyelid swelling or nystagmus). We also believe the Tono-Pen may play a valuable role in measuring the intraocular pressure of eyes in which accurate Goldmann applanation tonometry is not possible because of corneal edema and bullous keratopathy.

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OPHTHALMIC MINIATURE

So too in art: form is disclosed to the artist as he looks at what is over against him. He banishes it to be a "structure." This "structure" is not in a world of goods, but in this great world of men. It is certainly "there," even if no human eye seeks it out; but it is asleep.

Martin Buber, *I and Thou*Translated by Ronald Gregor Smith
New York, Charles Scribner's Sons, p. 41

The Value of Indices in the Central and Peripheral Visual Fields for the Detection of Glaucoma

C. Seamone, M.D., R. LeBlanc, M.D., M. Rubillowicz, M.D., C. Mann, M.D., and A. Orr, M.D.

We assessed 81 patients in four groups (normal, low- and high-risk ocular hypertension, and early glaucoma) with the standard Octopus G1 central visual field program in addition to two quantitative programs, PFN (peripheral and PFT (peripheral field-nasal) temporal), designed for this study to test the nasal and temporal periphery, respectively. Indices were calculated for each program for each subject in all groups. We then examined the behavior of the indices across the separate visual field areas within each group as well as the behavior of the indices of each field area among the different groups. We found that quantitative testing of the peripheral nasal visual field provided valuable information in the detection of glaucomatous visual dysfunction additional to that provided by quantitative testing of the central visual field. Quantitative testing of the temporal periphery was less valuable.

DETECTION OF visual field abnormalities in their earliest stage is the primary reason for performing perimetry in patients in whom glaucoma is suspected. Such information enables the clinician to initiate early treatment to prevent progression of, and perhaps reverse, visual loss.

Considerable effort has been aimed at identifying the earliest visual field defects that occur in glaucoma. When detected with manual perimetry, the classic early visual field changes are paracentral and arcuate scotomas, isolated peripheral nasal steps, and, uncommonly, temporal sector-shaped defects. ¹⁻⁵ With static threshold testing using the Goldmann and

Tübingen perimeters, Werner and Drance⁶ detected localized areas of scatter of threshold responses as a precursor to localized glaucomatous field defects. However, Quigley, Addicks, and Green⁷ showed that significant loss of axons can occur while results of light threshold kinetic perimetry remain relatively normal. Thus, it appears that even early field changes detected by the most exacting manual perimetric techniques are manifestations of a disease process already well underway.

The advent of automated static threshold perimetry has stimulated new interest in exploring the visual field for the purpose of defining early changes in glaucoma that remain undetected using manual techniques. For example, it has been shown that the earliest detectable change in the glaucomatous visual field is an increase in the localized short-term fluctuation while sensitivity remains normal.^{8,9}

Interpretation of visual field changes in glaucoma is facilitated and made more objective by the use of statistical data reduction to derive visual field indices. ¹⁰ Indices have been applied to the Octopus system by Flammer and coworkers. ¹¹ The indices of clinical importance are mean defect, short-term fluctuation, and corrected loss variance.

To date most of the work directed toward detection of early glaucomatous visual field changes has been devoted to the central field, with less attention paid to the periphery. LeBlanc, Lee, and Baxter, 12 using suprathreshold screening techniques in the nasal periphery in conjunction with quantitative central programs, reported that none of 96 eyes with primary open-angle glaucoma had peripheral nasal defects in the absence of a central field defect. From this study it might be reasoned that, in the presence of a normal quantitative central visual field study, suprathreshold testing of the nasal periphery is of little diagnostic value as it is not sensitive enough to pick up early nasal scotomas. However, when quantitative techniques were applied to the same area,

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Caprioli and Spaeth¹³ demonstrated peripheral nasal field defects in the absence of abnormalities of the central field in 11% of all eyes being evaluated for glaucoma. Thus, detailed quantitative testing of the nasal periphery may significantly improve the detection of early glaucomatous changes even in the presence of a normal quantitative central field.

Evaluation of the peripheral visual field might further be enhanced by the use of indices. While the range of normal values for indices in the central visual field is a part of the Octopus G1 program, such a range of normal values for indices in the peripheral visual field

does not yet exist.

We designed this study to establish a range of normal values for the indices mean defect, short-term fluctuation, and corrected loss variance in both nasal and temporal peripheral field areas; to compare the behavior of these indices in the central and peripheral field in normal subjects as well as those with ocular hypertension and primary open-angle glaucoma; and to assess the value of these indices in detecting visual field changes in the peripheral nasal and temporal areas.

Subjects and Methods

We recruited 81 subjects for this study. There were 60 men and 21 women. A medical history was obtained from each subject and a complete ocular examination was performed including refraction, slit-lamp examination, tonometry, and direct ophthalmoscopy. Each subject underwent central and peripheral visual field testing using the Octopus 201 perimeter.

The subjects were grouped according to four categories: normal; ocular hypertension, low risk; ocular hyptertension, high risk; and early primary open-angle glaucoma. Twenty-one normal subjects were recruited as normal controls. None had any history of ocular disease, trauma, or surgery. All were free of uncontrolled systemic disease. Both eyes had a best corrected visual acuity of 20/30 or better, normal (<22 mm Hg) intraocular pressure, and normal optic disks. Subjects were chosen to approximate an age spread of three subjects per decade from age 20 to 80 years.

For the ocular hypertension, low risk group, 20 subjects were chosen from our patient population according to the following criteria: open angles; no glaucomatous disk changes and no

other significant ocular abnormalities or systemic disease; and normal central visual fields as tested using the G1 program and interpreted without the use of visual field indices. Each eye included in the study had a documented intraocular pressure of >22 mm Hg on at least two separate visits and a best-corrected visual acuity of 20/30 or better. In each of these subjects, a clinical decision had previously been made that therapy was not required.

For the ocular hypertension, high risk group, another 20 subjects were chosen from our patient population using the same criteria as for the low-risk group, except that a clinical decision to treat had previously been made because

of significant risk factors.

For the early primary open-angle glaucoma group, 20 subjects with early primary openangle glaucoma were selected according to the following criteria: open angles, no history of ocular trauma, no ocular surgery, and no significant ocular disease (other than glaucoma) or uncontrolled systemic disease. Each eye studied had a visual acuity of 20/30 or better and an intraocular pressure of >22 mm Hg on at least two separate visits. In each subject, the G1 central visual field test was interpreted (without the use of visual field indices) as having definite, but early, visual field loss.

The study eye was selected randomly in subjects from the first three groups. In patients with early glaucoma, if only one eye was suitable for the study, then that eye was used; if both eyes were suitable, then the study eye was

chosen randomly.

Visual field examination—Each subject was tested using three visual field programs on the Octopus 201 perimeter (Figure). In each case, testing included both phase 1 and phase 2 (that is, each point tested twice) to enable the calculation of indices. The G1 program was used to test the central portion of the visual field (59 central points strategically placed within a radius of 26 degrees from fixation). The PFN program (peripheral field-nasal) was designed for this study to test the nasal peripheral field at 31 points located between 30 and 50 degrees from fixation at a maximum of 16 degrees above and below the horizontal meridian, with a grid density of 5 degrees horizontally and 4 degrees vertically. The PFT program (peripheral fieldtemporal) was designed for this study to mirror the PFN program, but over a slightly wider area, to test the temporal peripheral field at 32 points located between 30 degrees and 60 degrees from fixation at a maximum of 12 degrees above and below the horizontal meridian, with

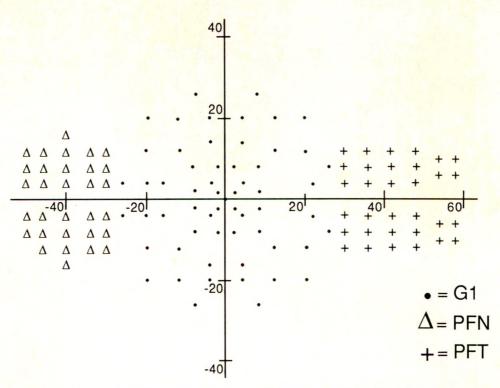


Figure (Seamone and associates). Areas tested by each visual field program in the right eye.

a grid density of 6 degrees horizontally and 4 degrees vertically.

Those subjects without previous experience with automated perimetry were allowed a brief test run to familiarize them with the test method. The G1 program was tested first in each subject, followed by PFN and PFT in random order. All patients were given adequate respite between tests. Corrective lenses were used for G1 testing where appropriate but not for either of the peripheral programs.

Calculation of indices—The mean defect, shortterm fluctuation, and corrected loss variance were calculated using the formulas of Flammer and associates. 11 The expected normal values for the threshold light sensitivities of the test locations and the age correcting factor needed for the calculation of each of the indices for Gl, PFN, and PFT were estimated using linear regression models on our pool of normal data.

Results

In general, the mean values of the indices (± S.D.) and field area (G1, PFN, PFT) increased as expected on the basis of clinical grouping

(normals, low-risk, high-risk, glaucoma) (Table 1).

Paired t-tests were performed to compare the mean values of the indices, within each of the subject groups, between the PFN and G1 and between the PFT and G1 field areas. In each case, Bonferroni's method was applied to adjust the individual P values for the number of comparisons made (two) to achieve an overall level of significance of P = .01 (Table 2).

The mean defect was not significantly different between either the PFN and G1 or between the PFT and G1 field areas within any of the subject groups. The short-term fluctuation, however, was significantly different between the PFN and G1 field areas within all of the groups; it was not significantly different between the PFT and G1 field areas within any group. The corrected loss variance was only significantly different between the PFT and G1 field areas, and only then within the groups with increased intraocular pressure (the lowrisk, high-risk, and glaucoma groups).

A post-hoc test of hypothesis was then used to assess the ability of the indices to distinguish between the different subject groups. Again, Bonferroni's method was applied to adjust each of the individual P values for the number of

TABLE 1
VISUAL FIELD INDICES ACROSS THE SEPARATE VISUAL FIELD AREAS

GROUP		NO. 05	MEAN D	MEAN DEFECT		SHORT-TERM FLUCTUATION		CORRECTED LOSS VARIANCE	
	FIELD	NO. OF EYES	MEAN	S.D.	MEAN	S.D.	MEAN	S.D.	
Normals	G1	21	0.000	1.084	1.420	0.220	1.341	1.254	
	PFN	21	0.052	1.450	1.841	0.489	1.636	2.962	
	PFT	21	-0.012	1.349	1.543	0.327	0.541	0.875	
Low-risk	G1	20	1.101	1.208	1.365	0.231	2.224	0.899	
	PFN	20	1.192	1.308	2.062	0.720	2.479	4.560	
	PFT	20	1.088	0.886	1.428	0.178	1.128	1.249	
High-risk	G1	20	1.298	1.304	1.519	0.270	2.347	1.606	
	PFN	20	1.840	1.892	2.374	1.097	2.195	2.685	
	PFT	20	0.909	1.632	1.682	0.635	0.728	0.616	
Glaucoma	G1	20	4.125	1.691	1.756	0.228	15.036	14.054	
A. S.	PFN	20	6.961	3.689	3.370	1.006	19.018	25.357	
	PFT	20	2.673	2.587	2.028	0.518	1.351	2.121	

comparisons made (six) to achieve an overall level of significance of P = .01 (Table 3).

The mean defect was significantly different between the glaucoma group and each of the other three groups (normal, low-risk, and highrisk) in both the PFN and G1 field areas; in the PFT field area, it was only significantly different between the normal and glaucoma groups. The short-term fluctuation was significantly different between the glaucoma and each of the other three groups in the G1 and PFN field areas; in the PFT field area, it was only significantly different between the normal and glaucoma groups and between the low-risk and glaucoma groups. The corrected loss variance was significantly different between the glaucoma and each of the other three groups in both

TABLE 2

PAIRS OF FIELD AREAS WITH STATISTICALLY
SIGNIFICANT DIFFERENCES IN INDICES, WITHIN
SUBJECT GROUPS*

	PAIRS OF	F	VALUE	BY GRO	UP
INDEX	FIELD AREAS	NORMALS	LOW	HIGH RISK	GLAUCOMA
Mean defect	PFN-G1	NS	NS	NS	NS
	PFT-G1	NS	NS	NS	NS
Short-term	PFN-G1	<.01	<.01	<.01	<.01
fluctuation	PFT-G1	NS	NS	NS	NS
Corrected	PFN-G1	NS	NS	NS	NS
loss variance	PFT-G1	NS	<.01	<.01	<.01

^{*}NS, not significant

the G1 and PFN field areas; in the PFT field area, it was not able to distinguish any of the groups from each other.

Discussion

The purpose of visual field indices is to describe in simple quantitative terms disturbanc-

TABLE 3

PAIRS OF GROUPS WITH STATISTICALLY SIGNIFICANT DIFFERENCE IN INDICES, WITHIN FIELD AREAS*

		PAII	IPS [†]	
INDEX	FIELD AREA	N-G	LR-G	HR-G
Mean defect	G1	<.01	<.01	<.01
	PFN	<.01	<.01	<.01
	PFT	<.01	NS	NS
Short-term	G1	<.01	<.01	<.01
fluctuation	PFN	<.01	<.01	<.01
	PFT	<.01	<.01	NS
Corrected	G1	<.01	<.01	<.01
loss variance	PFN	<.01	<.01	<.01
	PFT	NS	NS	NS

^{*}Group pairs normal-low risk, normal-high risk, and low riskhigh risk showed no significant difference in indices within field areas.

[†]G, glaucoma; HR, high risk; LR, low risk; N, normal; NS, not significant.

TABLE 4

NUMBER OF SUBJECTS WITH DISTURBED INDICES INCREMENTALLY DETECTED
BY THE THREE VISUAL FIELD TEST PROGRAMS*

INDEX	GROUP	NO. OF EYES	DETECTED BY G1	ADDITIONALLY DETECTED BY PFN	ADDITIONALLY DETECTED BY PFT	NORMAL INDEX IN ALL 3 AREAS
Mean defect	Low-risk	20	6	0	0	14
	High-risk	20	4	3	0	13
	Glaucoma	20	18	2	0	0
Short-term	Low-risk	20	0	3	0	17
fluctuation	High-risk	20	4	3	0	13
	Glaucoma	20	7	6	1	6
Corrected loss	Low-risk	20	2	1	3	14
variance	High-risk	20	6	1	0	13
	Glaucoma	20	18	2	0	0
Combined	Low-risk	20	6	3	2	9
indices	High-risk	20	8	3	0	9
	Glaucoma	20	19	1	0	0

^{*}Disturbed indices defined as visual field measurements exceeding the mean by at least 2 S.D.

es of a given visual field area. The mean defect is a numerical expression of the deviation from the expected age-corrected normal level of differential light sensitivity of a particular visual field area. It is most sensitive to generalized changes in sensitivity. The short-term fluctuation is an expression of the scatter of the differential light threshold sensitivities of the test locations when repeatedly measured during a visual field examination. It is affected to some extent by the alertness and attentiveness of the subject. It is also strongly affected by the level of differential light sensitivity itself, with regions of low sensitivity tending to show higher fluctuation. 9,14 A localized increase in the shortterm fluctuation in areas of normal sensitivity may be the earliest perimetric sign of glaucoma.9 The corrected loss variance is an expression of the magnitude of localized variations in the visual field, both depressions (scotomas) and elevations (hypersensitive test locations), adjusted for short-term fluctuation.

The mean values and standard deviations obtained in this study for the central region of the visual field (G1) for each of the subject groups are in agreement with the findings of another investigator (Flammer, unpublished data).

We drew three inferences about the comparison of the mean values of the indices across the different field areas. First, the mean defect was not significantly different between the PFN and G1 or between the PFT and G1 field areas for

any group of subjects. This suggests that it is rather homogeneous across the visual field. Second, the short-term fluctuation was significantly higher in the PFN field area than in the G1 field area within all groups of subjects. This may follow from the observation that between 30 and 60 degrees eccentricity, the slope of the hill of vision is steeper nasally than temporally; consequently, the short-term fluctuation in the peripheral nasal field would tend to be higher in this area of lower sensitivity. It was not significantly different between the PFT and G1 field areas within any group of subjects. Third, the corrected loss variance was significantly higher within subject groups with increased intraocular pressure (both ocular hypertensive groups and the glaucoma group) in the PFT field area than it was in the G1 field area. This may reflect the finding that visual field defects in the temporal field can be localized wedge defects.

Ultimately, the clinical question of concern to ophthalmologists is whether additional peripheral visual field testing increases the ability to identify patients with visual dysfunction. The number of subjects with disturbed (exceeding the mean by at least 2 S.D.) visual field indices incrementally detected by the three visual field programs (G1, PFN, and PFT) is summarized in Table 4.

As the initial examination, central (G1) visual fields identified most of the subjects with visual field dysfunction in most subject groups. It

Optic Atrophy in Children

Michael X. Repka, M.D., and Neil R. Miller, M.D.

We reviewed the records of 218 children in whom a diagnosis of optic atrophy had been made between 1978 and 1987. A cause for the atrophy was determined for 195 patients (89%). Tumor, the most frequent cause, was found in 63 patients (29%). The most common tumor was a glioma of the anterior visual pathway; it was found in 27 patients (43% of tumors; 12% overall). The second most frequently encountered tumor, a craniopharyngioma, was found in 14 patients. Inflammation, the second most common cause of optic atrophy, occurred in 38 children (17%). Trauma caused optic atrophy in 24 patients (11%). No cause could be found for 23 patients (11%). Thirteen patients were less than 1 year of age at the time of diagnosis. Three of these patients had tumors. One was a cerebral glioblastoma, and the other two were optic gliomas. The diagnosis of optic atrophy in infancy does not imply a benign cause.

THE VARIOUS CAUSES of optic atrophy in child-hood are well known, but the relative incidence of each cause is unclear. In 1968, Costenbader and O'Rourk examined a series of children with optic atrophy and were able to establish a diagnosis for only 50% of the patients they examined.

The present study was designed to determine the relative incidence of the causes of child-hood optic atrophy and to determine how often a diagnosis could be made since the advent of computed tomography and magnetic resonance imaging. These findings could then be used in counseling a patient's parents about the necessity and selection of diagnostic tests.

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Subjects and Methods

We reviewed the records of inpatients and outpatients in whom a diagnosis of unilateral or bilateral optic atrophy had been made by the neuro-ophthalmology and pediatric ophthalmology services of our institution between 1978 and 1987. Only patients younger than 18 years at the time of diagnosis were included. Clinical examination, computed tomography, magnetic resonance imaging, and laboratory studies including histopathologic findings when available were used to establish the diagnosis. The causes of optic atrophy were divided as follows: hereditary, intrauterine and neonatal disease, inflammation/infection, hydrocephalus (including pseudotumor cerebri), tumor, neurodegenerative disease, trauma, toxic and metabolic disease, miscellaneous, and no diag-

Results

We identified 218 children in whom the diagnosis of unilateral or bilateral optic atrophy had been made. A cause was determined for 195 patients (89%) (Table 1).

Tumor, the most frequent cause, was found in 63 patients (29%) (Table 2). The most common tumor was an optic glioma, found in 27 patients (43% of tumors; 12% overall). These patients had a mean age of 7.0 years (range, 0.25 to 16 years). The chiasm was affected in 19 of these patients (mean age, 7 years; range, 0.25 to 16 years), whereas optic nerve involvement (unilateral or bilateral) was found in only eight patients (mean age, 6 years; range, 0.75 to 12 years).

The second most commonly encountered tumor, a craniopharyngioma, was found in 14 patients (22% of tumors; 6% overall). The mean age of these patients was 8 years (range, 1.4 to 16 years).

Less commonly encountered intracranial tu-

TABLE 1

CAUSES OF CHILDHOOD OPTIC ATROPHY

(N = 218)

DIAGNOSIS	NO. OF PATIENTS	(%)	
Tumor	63	(29)	
Postinflammatory	38	(17)	
Trauma	24	(11)	
No diagnosis	23	(11)	
Hereditary	19	(9)	
Perinatal disease	18	(9)	
Hydrocephalus (without tumor)	14	(6)	
Neurodegenerative disease	11	(5)	
Toxic/metabolic disease	2	(1)	
Miscellaneous	6	(3)	

mors included pituitary adenoma (three cases), sphenoid ridge meningioma (one case), and suprasellar germinoma (one case). Posterior fossa and supratentorial tumors produced optic atrophy secondary to chronic papilledema in 13 patients.

Localized orbital tumors other than optic nerve glioma produced optic atrophy in seven patients (lymphoma in three cases, neuroblastoma in two cases, and one case each of cavern-

ous hemangioma and leukemia). The second most common cause of optic atrophy in children was inflammation. Optic atrophy occurred after optic neuritis in 32 children and after meningitis in six children. The mean age of patients with optic atrophy after optic neuritis was 13.8 years (range, five to 18 years). Patients who developed optic atrophy after meningitis had a mean age of 7 years (range, 0.25 to 15 years).

The third most frequently observed cause of optic atrophy was head trauma (24 patients). Hereditary optic atrophy was present in 19 patients (9%). Of the 19 patients, 12 (63%) had dominant optic atrophy and seven (37%) had Leber's optic neuropathy. Perinatal disease (prematurity, anoxia, intrauterine, or perinatal infection) was responsible for optic atrophy in 18 patients (9%). Hydrocephalus without evidence of intracranial tumor was present in 14 patients (6%).

Despite extensive initial evaluation, no cause of optic atrophy could be determined for 23 patients (11%). Ten of these patients have been followed up by us for a mean interval of 2.3 years. In each case, the cause of optic atrophy remains unknown.

TABLE 2
TUMORS PRODUCING OPTIC ATROPHY
(N = 63)

DIAGNOSIS	NO. OF PATIENTS	(%)
DIAGNOSIS	TAILING	
Optic glioma (chiasm)	19	(30)
Optic glioma (optic nerve)	8	(13)
Craniopharyngioma	14	(22)
Orbital mass	7	(11)
Other supratentorial tumors	7	(11)
Posterior fossa tumor	5	(8)
Pituitary adenoma	3	(5)

Optic atrophy was diagnosed in 13 patients before 1 year of age (Table 3). Of these 13 patients, five had a history of intrauterine infection, perinatal trauma, or marked prematurity. Three children in this group had tumors: a grade IV glioblastoma, a chiasmatic glioma, and an optic nerve glioma.

Discussion

The finding of optic atrophy in a child is always a cause for concern. In 1968, evaluation of optic atrophy in children determined a cause 50% of the time. Costenbader and O'Rourk found only one tumor, a craniopharyngioma, in their series of 63 patients. Rh factor incompatibility was responsible for five of their cases of optic atrophy. This was a diagnosis we did not make, presumably because of the nearly complete prevention of Rh isoimmunization by obstetric management with Rh immune globulin. The same strain of the sa

In this series of 218 children, a diagnosis was

TABLE 3
CAUSE OF OPTIC ATROPHY IN INFANTS LESS
THAN 1 YEAR OF AGE
(N = 13)

DIAGNOSIS	NO. OF PATIENTS	(%)
Unknown	5	(38)
Prematurity	3	(23)
Tumor	3	(23)
Perinatal trauma	1	(8)
Intrauterine infection	-1	(8)

made for 195 patients (89%). This improvement in diagnostic ability is probably related in part to the evolution of neuroimaging techniques and in part to a better understanding of some causes of optic atrophy (for example, Leber's optic neuropathy, dominant optic atrophy).

The most frequent cause of optic atrophy was tumor (63 patients, 29%). The most common tumor was optic glioma, found in 27 patients. Craniopharyngioma was the second most common tumor, occurring in 14 patients. The second most common cause of optic atrophy was inflammation in the form of meningitis or optic neuritis (38 patients, 17%). The third most frequent cause was head trauma (24 patients, 11%). Other frequently observed causes were perinatal disease and hydrocephalus. Hereditary optic atrophy was also common. Of all 218 patients with optic atrophy, 77 (34%) required medical intervention, surgery, or both. These patients all had intracranial tumors producing hydrocephalus.

The diagnosis of optic atrophy in infancy carries not only the prognosis of impaired vision for life, but also raises the specter of a serious, life-threatening disease. One widely used reference suggests that no cause can be found in most infants who have optic atrophy.6 Thirteen of our patients had a diagnosis of optic atrophy made before age 1 year. No diagnosis could be determined for five of these patients; however, in the other eight patients, optic atrophy was associated with marked prematurity (less than 31 weeks gestation), perinatal trauma, intrauterine infection, or tumor. The finding of an intracranial tumor in three of these infants (23%) confirms the need to evaluate fully even infantile optic atrophy.

The incidence of each cause of optic atrophy as determined in this review is subject to at least two biases. First, the patients in this study were seen in a referral setting, and may not represent the incidence in the community. It is likely that this bias increased the incidence of tumor in our series. Second, we believe that the incidence of optic atrophy associated with neurodegenerative syndromes may be underestimated in this study. In our experience, optic atrophy often develops late in the course of the patient's deterioration, and ophthalmologic consultation is therefore not always obtained.

A complete evaluation of infants and children with optic atrophy is essential. It should begin with a thorough prenatal and birth history, with particular reference to perinatal

trauma and prematurity (less than 31 weeks gestation). A history of significant head trauma, meningitis, or optic neuritis should be sought. Finally, a search for evidence of familial optic atrophy should be undertaken, including an examination of available family members. For patients with no contributory history, the chance of a tumor or hydrocephalus producing the optic atrophy was 45% in this series. These patients should undergo a neuroimaging study, either computed tomography or, preferably, magnetic resonance imaging. Whichever study is performed, it must include images of the optic nerves and chiasm and of the posterior fossa.

For all patients with optic atrophy, follow-up is prudent. These examinations will allow the physician to recommend appropriate optical aids and visual rehabilitative care. If progressive visual loss occurs, the patients must be completely reexamined, including neuroimaging. For patients with optic atrophy caused by tumor, careful ophthalmologic follow-up is invaluable for planning of treatment by oncologists, neurosurgeons, and radiation therapists. The input of the ophthalmologist may be crucial in the early detection of a recurrence.

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Echographic Characteristics of Benign Orbital Schwannomas (Neurilemomas)

Barry M. Byrne, B.A., W. A. J. van Heuven, M.D., and Andrew W. Lawton, M.D.

We examined two patients with orbital schwannomas (neurilemomas). The echographic findings, including a sharply outlined capsule, a well-defined central cystic space within the tumor with very low internal reflectivity surrounded by smaller cysts with variable reflectivity, slight or no compressibility, and blood flow, should help to differentiate these benign tumors from other orbital lesions. Histologic examination showed a combination of Antoni type A (dense and cellular) and Antoni type B (loose, edematous, or necrotic) patterns.

FROM January 1982 through December 1987, 198 orbital examinations were performed by the diagnostic ultrasound laboratory at our institution. Two of these examinations showed benign schwannomas. This agrees with the reported incidence of schwannomas comprising 1% of orbital tumors. ¹⁻³ The echographic findings in our two cases were so similar that the diagnosis of schwannoma in our second case was made by echography alone. ^{4,5}

Case Reports

Case 1

A 41-year-old man had a two-year history of headaches and a slowly progressive protrusion of the right eye. During the previous six months the proptosis had increased more rapidly. The patient also complained of double vision. Results of systemic examination were normal. No nodes were felt in the head or neck. Visual acuity was 20/20 in each eye. Extraocular movements were full. The right eye was displaced forward and temporally. Eyelid fissures were equal, with no eyelid lag or retraction. Intraocular pressure was 15 mm Hg in each eye. Results of ophthalmoscopy were normal with no cupping. The sensation of the right cheek (inferior orbital nerve) was slightly decreased. Supraorbital and corneal sensations were normal. Thyroid studies showed no dysfunction.

Computed tomography (Fig. 1) showed a mass in the right orbit, 2 × 2.5 cm in size, which did not enhance. It was located adjacent to the optic nerve and medial rectus muscle and it appeared to be separate from the optic nerve. Because of the lack of enhancement, the diagnosis of hemangioma was considered unlikely. The possibility of myositis was considered. The diagnostic ultrasound examination showed an orbital tumor located within the muscle cone, bordering but not attached to the optic nerve superiorly and nasally. The mass was 25 mm in

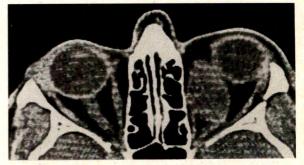


Fig. 1 (Byrne, van Heuven, and Lawton). Case 1. Axial computed tomographic scan performed with contrast media displays mass in the superonasal aspect of the right orbit.

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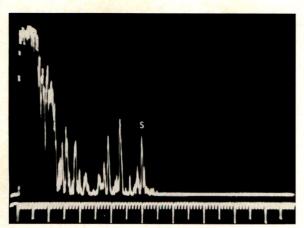


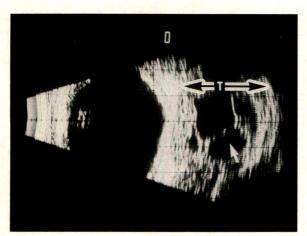
Fig. 2 (Byrne, van Heuven, and Lawton). Case 1. Paraocular A-scan shows a well-outlined posterior surface (S) of the tumor.

width, with the well-outlined posterior border 31 mm from the external eyelid surface in the supranasal quadrant (Fig. 2). Within the mass was a sharply outlined central space with low internal reflectivity. Surrounding this were smaller spaces, some of which showed low internal reflectivity, while others showed high to medium reflectivity with sound attenuation (Fig. 3). The mass had a hard-to-firm (slightly compressible) consistency and indented the globe slightly. Vascularization was noted on Doppler testing, but spontaneous vascular movements, indicative of blood flow on the standardized A-scan, were not seen. The echographic diagnosis was a sclerosed hemangioma or a schwannoma.

On the following day the orbital mass was removed through a superior orbitotomy. Pathologic studies showed an ovoid mass $3.8 \times 2 \times 1.5$ cm, with a smooth, bright yellow surface with areas of light brown and dark red-brown. On cross section, the central area showed cystic spaces filled with brown fluid. The frozen section diagnosis was a benign fibrous histiocytoma. The subsequent microscopic diagnosis was schwannoma (neurilemoma) (Fig. 4).

Case 2

A 66-year-old woman was examined because of decreased vision in the left eye for about five months and some pain around the eye for one month. Results of systemic examination were normal. Visual acuity was R.E.: 20/25 +2.00 sph and L.E.: 20/200 +3.00 sph. The patient's spectacles were R.E.: +2.25 sph and L.E.: +2.50 sph (indentation of left eye may have increased hyperopia). External examination showed xanthoma of the eyelids and dermatochalasis. Intraocular pressure was 20 mm Hg in each eye. There was a left relative afferent pupillary defect. The cup/disk ratio was R.E.: 0.4 and L.E.: 0.3. The left fundus showed horizontally oriented choroidal folds in the posterior pole. Hertel exophthalmometry measurements were R.E.: 14 mm and L.E.: 17 mm. Extraocular movements showed slight limitation in both horizontal directions and upwards in the left eye. Computed tomography (Fig. 5) showed a left orbital tumor extending into the apex of the orbit, without a clear view of the optic nerve.



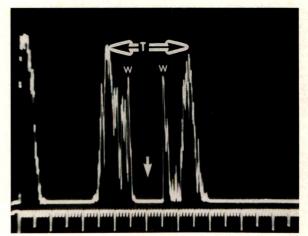


Fig. 3 (Byrne, van Heuven, and Lawton). Case 1. Left, Transocular B-scan shows tumor (T) with large cystic space centrally (arrow). Right, Transocular A-scan shows tumor with large cystic space centrally (arrow). Note the steeply rising spikes within the tumor produced by the cyst walls (W) and the low reflectivity compared with the surrounding tumor tissue.





Fig. 4 (Byrne, van Heuven, and Lawton). Case 1. Left, Encapsulation (large arrow) of the lesion, central necrosis and cyst formation (small arrow) along with foci of hemorrhage (hematoxylin and eosin, ×32). Right, Admixing of tightly packed Antoni type A fibers (arrow) with looser, degenerating Antoni type B fibers (arrowhead) and sclerotic, thick-walled blood vessels (hematoxylin and eosin, ×130).

The clinical differential diagnosis included meningioma, schwannoma, lymphangioma, hemangioma, and glioma.

Diagnostic ultrasound showed a left orbital tumor filling the muscle cone. The tumor bordered the left optic nerve temporally and extended from 4 mm posterior to the sclera to the orbital apex. It did not appear to be adherent to the optic nerve. The recti muscles in the left orbit were thicker than those in the right orbit by 1.0 to 1.5 mm. The mass was well outlined (Fig. 6) and hard (noncompressible), with a

sharply outlined central space with very low internal reflectivity, surrounded by smaller spaces of low to medium reflectivity (Fig. 7). Doppler testing did not show blood flow, but standardized A-scan showed spontaneous movements along the septa, indicating blood flow. The left optic nerve measured 0.8 mm less than the right optic nerve (right = 3.2 mm, left = 2.4 mm). Because of the similarity of these findings to the findings three years previously in Case 1, the echographic diagnosis of schwannoma (neurilemoma) was made. Two

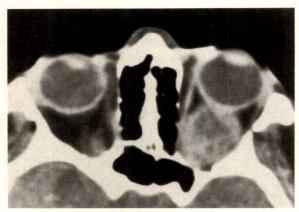


Fig. 5 (Byrne, van Heuven, and Lawton). Case 2. Axial computed tomography performed with contrast media displays mass filling retrobulbar space.

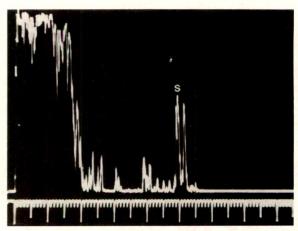
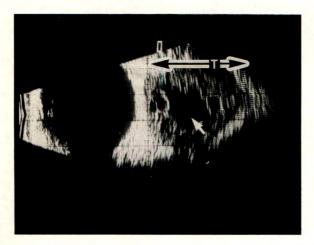


Fig. 6 (Byrne, van Heuven, and Lawton). Case 2. Paraocular A-scan shows a well-outlined posterior surface (S) of the tumor.



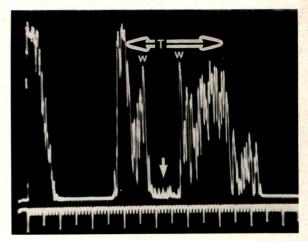
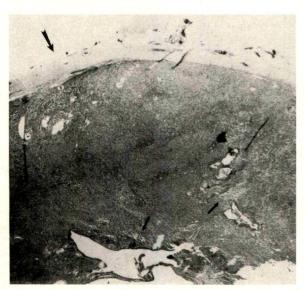


Fig. 7 (Byrne, van Heuven, and Lawton). Case 2. Left, Transocular B-scan shows tumor (T) with large cystic space centrally (arrow). Right, Transocular A-scan shows tumor with large cystic space centrally (arrow). Note steeply rising spikes within the tumor produced by the cyst walls (W) and the very low reflectivity within compared with the surrounding tumor tissue. A-scan is set at tissue sensitivity +6 dB.

months later, the tumor was surgically removed through a transfrontal craniotomy. The surgical appearance was a well-encapsulated tumor that was clinically thought to be a dermoid cyst. Pathologic examination showed a mass measuring $22 \times 18 \times 12$ mm that was bright yellow on its cut surface, with focal areas of dark red discoloration. The pathologic diagnosis was schwannoma (neurilemoma) (Fig. 8).

Discussion

Schwannoma (neurilemoma) is a neoplasm that can occur wherever Schwann cells are present, that is, in any myelinated peripheral nerve. In the orbit, schwannomas originate from sensory nerves, tend to occur during middle age, are located behind the globe, grow



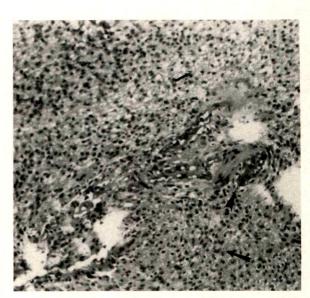


Fig. 8 (Byrne, van Heuven, and Lawton). Case 2. Left, Encapsulation (large arrow), foci of lipid deposition, and hemorrhagic necrosis (small arrows), which are classic signs of schwannoma (hematoxylin and eosin, × 25). Right, On higher power photograph, abnormal blood vessels (arrowhead), hemorrhage, and intermingled Antoni type A (large arrow) and type B (small arrow) areas are clearly seen (hematoxylin and eosin, × 130).

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slowly, and may be painful. The tumor begins focally in a nerve and enlarges in a nodular fashion to become an encapsulated mass covered by stretched perineural cells.² It may be independent or associated with neurofibromatosis. However, neurofibromas of the orbit are not encapsulated.

Although our two patients both had intraconal masses, schwannoma may occur anywhere in the orbit. When they occur within the muscle cone, they may simulate optic neuritis. 1,2 Malignant transformation is rare. 1,2

Pathologically, schwannomas classically show a mixture of two patterns, the Antoni type A fascicular dense (cellular) pattern and the Antoni type B looser (edema, necrosis) pattern containing cells suspended in mucinous material originating from the basement membrane. Occasionally, these mucinous areas are cyst-like and hemorrhages may occur within them.

The echographic findings in both our patients can be explained by the typical pathologic features of orbital schwannoma, including a capsule around the tumor, central cystic spaces of low reflectivity (Antoni type B areas) with sharply outlined cyst walls, and surrounding areas of medium to high reflectivity (Antoni type A areas). Orbital tumors, such as lymphangiomas and hemangiomas, may also contain cystic spaces, although the typical echographic

appearance should make it possible to diagnose these orbital tumors correctly before surgery. During surgery, the typical appearance of schwannoma should also lead to the correct surgical diagnosis.

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OPHTHALMIC MINIATURE

When Chloris's eyes came up to meet Lulu's, Lulu imagined that she could see in their depths that same twisted blue light, the little corruptive blue flame that invariably shone out of the girl's irises whenever she came to Lulu with secret intelligences about her brother.

Raymond Kennedy, Lulu Incognito New York, Vintage Contemporaries (A Division of Random House), 1988, p. 208

Progression of Visual Defects in Ischemic Optic Neuropathy

Lanning B. Kline, M.D.

Six patients with nonarteritic ischemic optic neuropathy experienced worsening of visual acuity and field loss during the six-week period after onset (range, three to six weeks), without apparent ophthalmoscopic changes. Thereafter, visual function remained unchanged. Various medications were used, but none prevented deterioration of visual function. Although not a widely recognized phenomenon, progression of visual deficit occurred in these patients in the early weeks after onset of ischemic optic neuropathy.

ISCHEMIC OPTIC NEUROPATHY is characterized by sudden, painless, usually irreversible loss of visual function, an afferent pupillary defect, and optic disk edema. Affected individuals are typically between 45 and 80 years of age. Pathologically, there is ischemic infarction within the laminar portion of the optic nerve. The cause of nonarteritic ischemic optic neuropathy is uncertain. About half of affected patients have hypertension, but the remainder lack any specific disease.

The ophthalmologic literature emphasizes the nonprogressive course of visual loss in ischemic optic neuropathy. ¹⁻⁶ However, in some patients there is definite deterioration of visual function early in the clinical course. ^{7,8} Herein I describe six patients with progressive visual loss within six weeks of onset of ischemic optic neuropathy. These patients, who ranged in age from 55 to 71 years, were all referred for neuro-ophthalmic examination. There were three men and three women (Figs. 1 and 2). Two cases are presented in detail.

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Case Reports

Case 1

A 63-year-old woman awoke one morning with a "blurred area" in the superior portion of her right visual field. There was no associated periocular pain or headache, and the patient was taking no medications regularly. One week later she consulted her ophthalmologist, who diagnosed right ischemic optic neuropathy.

Two weeks after the onset of visual symptoms, visual acuity was R.E.: 20/20 and L.E. 20/15. Results of color vision testing were normal in each eye, but there was a right afferent pupillary defect. Eye movements and results of slit-lamp examination were normal. The left visual field was unremarkable, whereas the right visual field showed a superior nerve fiber bundle defect (Fig. 1). The left optic disk was normal, and the right was swollen (Fig. 3). Westergren erythrocyte sedimentation rate was 15 mm/hour.

Nine days later (23 days after onset), visual acuity in the right eye had decreased to 20/50; five weeks later it was 20/200. At this time, the patient could no longer recognize any of the Ishihara pseudoisochromatic color plates with the right eye, and the right visual field showed a superior altitudinal defect with involvement of central fixation (Fig. 1). The right optic disk became pale.

Results of high resolution computed tomography were normal. After four years of followup, visual acuity has remained stable at R.E.: 20/200 and L.E.: 20/15.

Case 4

A 64-year-old woman suddenly lost a portion of the left central visual field. There was no associated pain, and she waited three weeks "hoping it would get better on its own" before consulting an ophthalmologist. At that time, visual acuity was R.E.: 20/25 and L.E.: 20/30. There was a left afferent pupillary defect, a

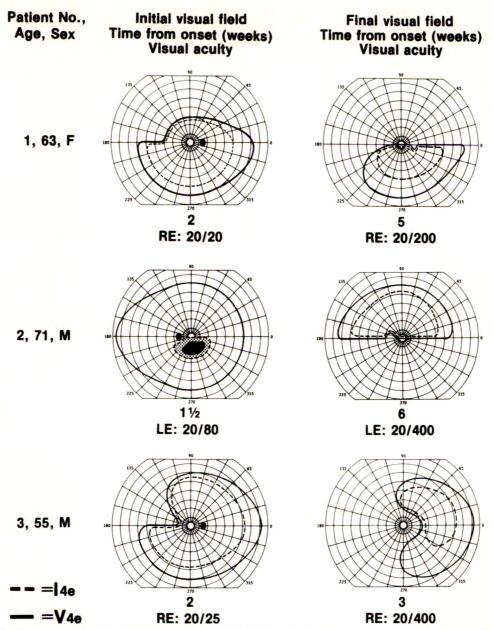


Fig. 1 (Kline). Summary of clinical data and visual fields for Patients 1, 2, and 3.

cecocentral scotoma in the left visual field (Fig. 2), and diffuse edema of the left disk.

One year previously the patient experienced transient right arm numbness and weakness. She had been taking aspirin and dipyridamole regularly since that time.

Westergren sedimentation rate was 30 mm/ hour, and results of complete blood cell count, prothrombin time, partial thromboplastin time, and skull x-rays were normal.

Five weeks after onset, visual acuity was R.E.: 20/25 and L.E.: 20/80. The left visual field

showed extensive superior and central loss (Fig. 2). The left disk was swollen, with exudates in the papillomacular bundle. Over the next five months, visual acuity in the left eye remained 20/80 and the left disk became pale.

Discussion

Progression of visual loss early in the course of ischemic optic neuropathy has received little

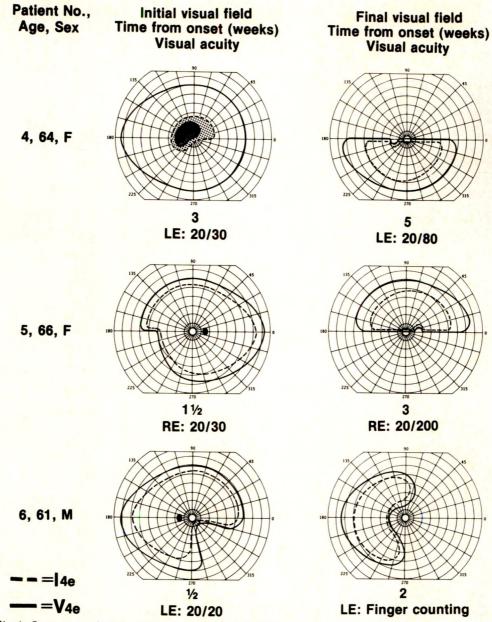


Fig. 2 (Kline). Summary of clinical data and visual fields for Patients 4, 5, and 6.

attention. Miller and Smith, who first applied the term ischemic optic neuropathy to the clinical syndrome, described progression of visual loss in one of 11 patients. In their patient, visual acuity decreased from 20/30 to 20/70, but the time course was not discussed. In 1973, Ellenberger, Keltner, and Burde³ reported no change in vision in most of their 48 patients, improvement in one third, and deterioration in two patients. No further data were given regarding these last two cases.

Clinical progression of ischemic optic neu-

ropathy was discussed by Boghen and Glaser in their review of 42 patients. In that series, visual field data were available in 34 patients, 11 (30%) of whom had progressive worsening over a period of several days to four weeks. Two illustrative cases were reported. A 61-year-old man had an initial visual acuity of 20/15 in the right eye, an inferior altitudinal defect, and swelling of only the superior aspect of the right disk. Within three weeks, visual acuity had decreased to counting fingers at 3 feet, with diffuse right optic disk edema. The second

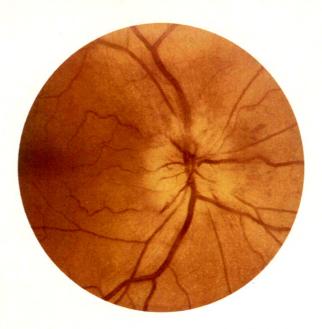


Fig. 3 (Kline). Case 1. Diffuse right optic disk edema two weeks after onset of ischemic optic neuropathy.

patient was a 63-year-old man with a visual acuity of 20/20 in the right eye and a swollen disk temporally. Within two weeks, visual acuity had decreased to counting fingers at 6 feet and the nerve head was diffusely swollen.

Shults⁸ described a 39-year-old man who developed bilateral consecutive ischemic optic neuropathy; visual loss progressed over about one week in each eye. Although there was no mention of progressive loss of visual function in ischemic optic neuropathy in his monograph,⁴ Hayreh⁹ has subsequently stated that "visual loss is usually non-progressive, but occasionally may be progressive for several hours or days."

Beck and coworkers10 reported recurrent episodes of ischemic optic neuropathy in the same eye. Of the four patients described, three experienced visual deterioration from one to three weeks after the initial episode. They all had segmental edema of the superior portion of the disk, which progressed to encompass the inferior aspect as well with concurrent loss of visual acuity and field. The fourth patient, a 52-year-old man, experienced recurrence of diffuse disk edema 45 months after his initial attack of ischemic optic neuropathy in the same eye. Visual field loss progressed from an inferior nerve fiber bundle defect to a complete inferior altitudinal defect, and visual acuity decreased from 20/25 to 20/100. The authors believed that their cases represented a second episode of ischemic optic neuropathy that

should be distinguished from progression within a single episode.

The patients described herein most closely resemble those described by Boghen and Glaser⁷ and Shults. 8 They all initially had a swollen disk on the involved side and had decreasing visual acuity and progression of their field defect within six weeks after onset of the initial episode. There were no apparent ophthalmoscopic changes during the period of visual decline, nor any clues that progression might occur. Shults8 emphasized the difficulty in assessing visual function using ophthalmoscopy. Two patients in this study (Cases 2 and 3) were unaware of further loss of vision. In four cases (Cases 1, 3, 5, and 6), initial field loss was characterized by a nerve fiber bundle defect, and with progression to involve the papillomacular bundle, there was an associated decline in visual acuity. Cecocentral scotomas, the initial manifestation in two patients, subsequently progressed to involve either the superior (Case 4) or inferior (Case 2) field.

No patients in the present series, nor in any previously reported with clinical progression, were found to have giant cell arteritis. Rather, all were believed to have the arteriosclerotic form of ischemic optic neuropathy.

The origin of clinical progression in ischemic optic neuropathy is unknown. Its basis may lie in the dissociation observed in ischemic optic neuropathy between the appearance of optic disk edema and decline in visual function. Boghen and Glaser⁷ described a 63-year-old woman who had simultaneous bilateral disk swelling, yet noted acute loss of vision only in the right eye. Two weeks later, vision decreased rapidly in the left eye. Hayreh¹¹ described four patients with ischemic optic neuropathy in whom optic disk edema preceded loss of visual acuity or field by two weeks to seven months. Six other patients have been described with asymptomatic optic disk edema that progressed to sudden visual loss after three days (one case),12 two to six months (four cases),13 and at a later date (one case). 14 There appears to be a spectrum in the onset of visual loss in ischemic optic neuropathy (Fig. 4). Hayreh¹¹ speculated that this may be related to the degree of optic disk ischemia. Thus, in eyes with ischemic optic neuropathy and preserved central visual acuity, ischemia causes only optic disk edema because of axoplasmic flow stasis. In more severe instances, ischemia also interferes with visual impulse transmission, with a corresponding loss of visual acuity.

A variety of treatment modalities have failed to prevent progression of visual loss in ische-

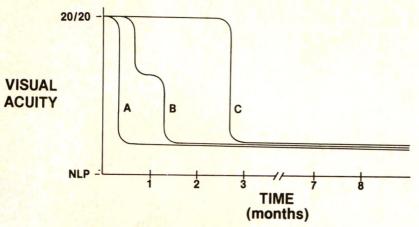


Fig. 4 (Kline). Three different patterns of visual loss that may occur with an episode of ischemic optic neuropathy. NLP, no light perception.

A = abrupt, nonprogressive visual loss

B = initial mild visual loss with progression

up to 6 weeks

C = abrupt visual decline between 1-7 months

mic optic neuropathy. One patient described by Boghen and Glaser⁷ was treated with three retrobulbar injections of corticosteroids, and another was already anticoagulated (warfarin). Three of the patients in this study were being treated with platelet antiaggregants (aspirin or dypyridamole), one with a beta-blocker (propranolol), and one with systemic corticosteroids (prednisone). At this time, there is no medication known to prevent this progressive course.

Awareness of the potential for visual worsening in ischemic optic neuropathy will eliminate unnecessary patient examination. Three patients in the present series underwent radiographic examinations (skull x-rays and cranial computed tomography), one underwent carotid Doppler studies, and one, a temporal artery biopsy, despite lack of symptoms suggestive of giant cell arteritis and a Westergren erythrocyte sedimentation rate of 2 mm/hour.

The ophthalmologist should use caution in relaying information regarding visual prognosis to a patient with ischemic optic neuropathy. It seems prudent to defer making a prognosis until six weeks after onset of visual loss.

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Nasolacrimal Drainage System Obstruction After Orbital Decompression

Stuart R. Seiff, M.D., and Norman Shorr, M.D.

We reviewed 123 cases of orbital decompression in 63 patients with dysthyroid ophthalmopathy. Of 90 cases of transantral ethmoidal orbital decompression, 14 (16%) resulted in epiphora. The tearing began between 11 and 18 months after surgery. All patients had obstruction distal to the common internal punctum. The delayed onset suggested progressive cicatricial obstruction of the nasolacrimal drainage system. Damage to adjacent tissues probably caused scarring to extend into the system.

INDICATIONS FOR orbital decompression in patients with dysthyroid ophthalmopathy include proptosis with corneal exposure, 1-3 compressive optic neuropathy, and cosmesis.4,5 Several surgical techniques have been described, including the transantral ethmoidal approach to the floor and medial wall of the orbit, the transeyelid or transconjunctival approach to the orbital floor and medial wall of the orbit, the lateral wall orbital decompression, and the "three wall" decompression, which combines the lateral and transantral ethmoidal methods.1 Complications include diplopia,6,7 blindness, cerebrospinal fluid rhinorrhea, persistent oroantral fistulae, and a little recognized complication of epiphora caused by nasolacrimal drainage system obstruction.3,8

We reviewed the records of an experienced orbital surgeon (N.S.) to determine the incidence of nasolacrimal drainage system obstruction and its clinical characteristics after orbital decompression in patients with dysthyroid ophthalmopathy.

Patients and Methods

We reviewed the most recent 123 orbital decompressions in 63 patients with dysthyroid ophthalmopathy performed by one of us (N.S.). The indications for surgery were exposure keratopathy (46 cases), compressive optic neuropathy (28 cases), and cosmesis (49 cases). Forty-two patients underwent 84 transantral ethmoidal decompressions, four patients underwent six three wall orbital decompressions, and 17 patients underwent 33 transconjunctival orbital decompressions.

The transantral ethmoidal decompression was begun after the gingivae, anterior wall of the maxillary antrum, and ethmoid sinuses were infiltrated with 1% lidocaine containing 1:100,000 epinephrine and hyaluronidase. The nose was packed with gauze soaked in 4% cocaine. The gingivae were then incised as for a standard Caldwell-Luc operation, using a cutting cautery. Periostium was then elevated bluntly upward until the infraorbital foramen was identified. Using an osteotome and mallet, the anterior wall of the maxillary antrum was fractured and rongeurs were used to create the bony ostomy. The mucosa of the sinus was removed at least superiorly and medially. The inferior portion of the nasolacrimal drainage system was identified and avoided. The ethmoidectomy was then performed using Takahashi forceps. After the ethmoidectomy was completed, attention was directed to the bony buttress formed by the junction of the orbital floor and medial wall. Bone removal was initiated by using a rongeur, after which the soft medial wall of the orbit was removed carefully so as to preserve the periorbita intact. The orbital floor was removed to the region of the infraorbital nerve. The infraorbital nerve was then disencased and allowed to hang free.

Once the bony structure had been removed, attention was directed to the periorbita. Using a No. 12 blade, the superior posterior periorbita of the medial orbit was cut. It is critical to

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perform the superior posterior cuts first to facilitate visualization in later steps in the procedure. If compressive optic neuropathy is present, it is imperative to cut extensively near the apex of the orbit in order to relieve compression of the nerve by the enlarged extraocular muscles. After the medial wall periorbita was stripped, the inferior periorbita was cut, with further prolapse of orbital fat. The nasal packing was removed and a nasoantral window was created. This has traditionally been considered necessary in antral surgery to enhance drainage and prevent postoperative mucocele formation. An accepted technique includes passing a curved hemostat through the lateral wall of the nose along the nasal floor into the maxillary antrum.9 The hemostat was then gently spread and a rongeur was introduced through the antrostomy to enlarge the nasoantral window to approximately 1.5 cm in size. The extreme inferior position is desirable in an effort to avoid the opening of the nasolacrimal duct below the inferior turbinate. A No. 16 French Foley catheter was then passed into the antrum and the balloon inflated with saline. The gingival incision was closed using a running 3-0 chromic suture.

The three wall decompression was performed in a manner similar to that just described for the transantral ethmoidal decompression; however, the lateral rim of the orbit was also removed in the routine manner for a lateral orbitotomy. Once the bone flap had been removed, the remaining posterior lateral wall was removed with a rongeur. Portions of lateral wall posterior to the rim on the bone flap were also removed. The lateral orbital rim was then wired back into position, leaving the bony defect posterior to it.

The transconjunctival approach to the orbital floor and medial wall of the orbit was performed after infiltration of the orbital floor and ethmoid sinuses with 1% lidocaine containing 1:100,000 epinephrine and hyaluronidase. The nose was packed with gauze soaked in 4% cocaine. A lateral canthotomy was performed with lysis of the inferior limb of the lateral canthal tendon. This allowed the lower eyelid to be rotated inferiorly, providing better exposure. An infratarsal incision was made from the conjunctival surface through the retractors of the lower eyelid to the level of the orbital septum. The dissection was carried inferiorly between the orbital septum and orbicularis muscle to the inferior orbital rim. This dissection plane minimizes prolapsing orbital fat and

maximizes subsequent visibility. At the inferior orbital rim, a periosteal incision was made. The periosteum of the rim was raised using a periosteal elevator and then continued posteriorly, elevating periorbita. The periorbita was elevated along the orbital floor and up onto the medial wall. A bony ostomy was created medial to the infraorbital nerve, using an osteotome and mallet. The bony orbital floor and medial wall of the orbit were removed using rongeurs. Care was taken to prevent damage to the infraorbital nerve as it was disencased. After the floor had been removed, the ethmoidectomy was performed using Takahashi forceps. When the ethmoidectomy was completed, the periorbita was cut with scissors and pulled free with bayonet forceps. Orbital fat and contents were allowed to prolapse into the ethmoid and maxillary antral spaces. The periorbita was then closed to periosteum anteriorly using an absorbable suture. The conjunctiva was closed using interrupted 6-0 plain sutures. The lateral canthus was then reattached to the periosteum of the lateral orbital rim. In this series, nasoantral windows were not created with this method of decompression.

The transconjunctival method was used when a moderate decrease in proptosis was desired and there was no evidence of compressive optic neuropathy. The transantral ethmoidal decompression was used when a more significant reduction in proptosis was desired or there was evidence of compressive optic neuropathy. This approach provided the surgeon with the best view of the orbital apex. The three wall decompression was used when maximal reduction of proptosis was desired.

Results

All patients with compressive optic neuropathy underwent transantral orbital decompression and had definite improvement in vision or in other signs of optic nerve function. No patients required reoperation for continued visual deficit after their regimen of corticosteroids was tapered. However, one patient suffered decreased vision after an initial improvement and, because of corticosteroid intolerance, underwent radiation therapy. She regained a visual acuity of 20/25. No patients lost vision as a result of orbital decompression.

Patients who underwent three wall orbital decompression averaged a 7.75-mm reduction

in proptosis (S.D., 3.89 mm; range, 5 to 10.5 mm), those undergoing transantral ethmoidal decompressions averaged a 4.81-mm reduction (S.D., 1.75 mm; range, 0 to 8.5 mm), and those undergoing transconjunctival decompressions a 4.27-mm reduction (S.D., 1.92 mm; range, 1.5 to 9.5 mm).

The most common complication was induced diplopia with the transantral ethmoidal decompressions. Of the ten previously unaffected patients, five developed diplopia in primary position. Of the 11 previously unaffected patients who underwent transconjunctival decompression, one developed diplopia (Table 1).

Two patients developed cerebrospinal fluid rhinorrhea after transantral ethmoidal decompression and one after transconjunctival decompression. All cases resolved spontaneously. One patient developed a postoperative antral hematoma that required evacuation. Three patients who underwent transantral ethmoidal orbital decompressions developed oroantral fistulae, which required surgical closure (Table 1). No complications were noted in those patients who underwent three wall orbital decompressions.

Tearing developed after 14 transantral ethmoidal orbital decompressions. It began in all cases between 11 and 18 months after the procedure. Seven lacrimal systems had complete obstruction distal to the common internal punctum, as evidenced by no passage of irrigant into the nose and reflux of fluid through the opposite punctum. Seven systems had a

partial obstruction, allowing a small amount of irrigant to pass into the nose with most of it refluxing. There were two cases of acute dacryocystitis. Ten dacryocystorhinostomies were performed with relief of symptoms. Lacrimal intubation with silicone tubes was performed without dacryocystorhinostomy in two cases of partial obstruction, with relief of symptoms. Two systems were not operated on (Table 2).

In this study, patients with severe dysthyroid ophthalmopathy (optic nerve compression, proptosis, and strabismus) tended to undergo transantral ethmoidal decompressions. Therefore, it should not be inferred that this procedure has an inherently higher complication rate than the other approaches to orbital decompression.

Discussion

The patients in this series were operated on by a surgeon experienced in orbital decompression who used well-accepted techniques. Despite these factors, the incidence of nasolacrimal duct obstruction was 16% in patients who underwent transantral ethmoidal decompression. In DeSanto's series, the incidence of nasolacrimal duct obstructions was approximately 2%. The reasons for the difference between the two series is unclear. Poor surgical technique is possible but unlikely. The surgeon had performed many orbital decompressions

TABLE 1
INCIDENCE OF COMPLICATIONS BY TYPE OF PROCEDURE

	TRANSANTRAL ETHMOIDAL AND THREE WALL (N = 90)*		TRANSCONJUNCTIVAL (N = 33)		TOTAL (N = 123)	
COMPLICATION	NO. OF PATIENTS	(%)	NO. OF PATIENTS	(%)	NO. OF PATIENTS	(%)
Diplopia induced	5 [†]	(50)	1 [‡]	(9)	6	(29) [§]
Nasolacrimal drainage obstruction	14	(16)	0	(0)	14	(11)
Oroantral fistulae	3	(3)	0	(0)	3	(2)
Cerebrospinal fluid rhinorrhea	2	(2)	1	(3)	3	(2)
Hematoma	1	(1)	0	(0)	1	(1)
Thyroid storm	1	(1)	0	(0)	1	(1)
Decreased vision	0	(0)	0	(0)	0	(0)

^{*}Three wall decompressions (n = 6) are included since transantral ethmoidal decompression is a part of this procedure.

Only ten patients at risk.

[‡]Only 11 patients at risk.

Based on 21 patients at risk.

TABLE 2

NASOLACRIMAL DRAINAGE SYSTEM OBSTRUCTION AFTER TRANSANTRAL ORBITAL DECOMPRESSION*

NO.	FINDING	NO. OF MOS POSTOPERATIVE	TYPE OF OBSTRUCTION	INTERVENTION	RESULT
1	Tearing	11	Complete	Dacryocystorhinostomy	Improved
2	Tearing	11	Complete	Dacryocystorhinostomy	Improved
3	Tearing	18	Complete	Dacryocystorhinostomy	Improved
4	Tearing	18	Partial	Dacryocystorhinostomy Dacryocystorhinostomy and antibiotics	Improved Improved
5	Dacryocystitis	11	Complete		
6	Dacryocystitis	11	Complete	Dacryocystorhinostomy and antibiotics	Improved
7	Tearing	12	Complete	Dacryocystorhinostomy	Improved
8	Tearing	12	Complete	Dacryocystorhinostomy	Improved
9	Tearing	12	Partial	Dacryocystorhinostomy	Improved
10	Tearing	12	Partial	Dacryocystorhinostomy	Improved
11	Tearing	11	Partial	None	No change
12	Tearing	11	Partial	None	No change
13	Tearing	12	Partial	Intubation with silicone tubing	Improved
14	Tearing	12	Partial	Intubation with silicone tubing	Improved

^{*}In all cases the location of the obstruction was distal to the common internal punctum.

before this series using standard, accepted techniques. Another possibility is that damage to the nasolacrimal duct is a more common complication of a well-performed transantral ethmoidal orbital decompression than previously recognized. Many orbital decompressions for dysthyroid ophthalmopathy are performed by otolaryngologists. The patients are then often followed up by ophthalmologists. In this setting, future tearing might well be attributed to dry eyes or corneal exposure from eyelid malpositions (common in dysthyroid ophthalmopathy), rather than to a postoperative lacrimal obstruction.

Irrigation of the lacrimal system of all affected patients demonstrated a complete or partial obstruction distal to the common internal punctum. Epiphora occurred only in patients who underwent transantral orbital decompressions. Therefore, the lesion was probably in an area affected by the transantral, rather than the transconjunctival, decompression.

Anatomic studies in cadaver dissections demonstrate that the proximal portion of the lacrimal system lies anterior to the surgical field (Fig. 1), making this region unlikely to be involved.

Conversely, the distal portion of the system lies more posteriorly along the transantral sur-

gical approach (Fig. 2). This area of the system could easily be injured in gaining access to the ethmoid sinuses.

The nasoantral window may represent a site

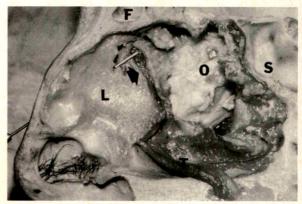


Fig. 1 (Seiff and Shorr). Transantral orbital decompression dissection on hemisected cadaver head. Latex has been injected into the lacrimal drainage system. Orbital contents have been decompressed (O). Note the surgically safe anterior position of the proximal portion of the lacrimal drainage system. The probe points to the lacrimal sac (via an iatrogenically created passage) and the arrow identifies the proximal nasolacrimal duct. F, frontal sinus; L, lateral wall of the nose; S, sphenoid sinus; T, reflected inferior turbinate.



Fig. 2 (Seiff and Shorr). Transantral orbital decompression dissection on hemisected cadaver head. Note the proximity of the distal lacrimal drainage system (arrow) to the operative field (finger).

of possible trauma to the lacrimal system. No cases of obstruction were noted in the transconjunctival decompressions and no nasoantral windows were performed in these cases. Cies and Baylis¹¹ and DeSanto³ reported rare nasolacrimal drainage system obstruction after Caldwell-Luc procedures. They speculated that the problem arose as a result of the nasoantral window. Cies and Baylis found that injury could occur to Hasner's valve from poorly placed, high nasoantral windows or from wellplaced windows in patients with low Hasner valves. In the surgical cases included in this study, the nasoantral windows were placed as far inferiorly as possible along the nasal floor to avoid the opening of the nasolacrimal duct below the inferior turbinate. Despite this care, nasolacrimal duct obstruction occurred.

The clinical onset of epiphora universally occurred between 11 and 18 months. This suggests that a slow, cicatricial process may be responsible for the obstruction to the lacrimal system, perhaps originating from damage to adjacent tissues. The distal lacrimal system is close enough to the surgical field that tissues adjacent to the system could be damaged (Fig. 2). Scarring extending from these tissues might well involve the duct or Hasner's valve, leading to obstruction. Thus, care should be taken during the decompression to avoid the duct itself and its adjacent tissues.

Several suggestions seem appropriate for possibly avoiding intraoperative trauma to these structures in the future. The distal nasolacrimal duct lies along the medial wall of the antrum during the decompression. It may interfere with access to the ethmoid air cells.

Great efforts should be made to identify and avoid damage to this structure or its surrounding bony canal. Fractures to the canal could conceivably contribute to scarring of the membranous duct within.

Hasner's valve is in the most jeopardy during the placement of the nasoantral window, as already described. The placement of the window is critical and should be performed inferiorly on the floor of the nose. This might help prevent direct damage in many cases. However, in view of a possible cicatricial process, it would be desirable to place the nasoantral window with as little mucosal injury and fracture extension as possible. Typically, the nasoantral window was placed with a closed hemostat pushed from the nose into the antrum and gently spread (Fig. 3).9 As the tip is blunt, this might cause nasal mucosal tears and the spreading might cause fracture lines distal to the actual window site. This could possibly contribute to late scarring. An alternative method is to use a nasal rasp (Fig. 4). Although the instrument does not look delicate, its sharp point and gently increasing diameter might provide a larger, less traumatic nasoantral window, decreasing the chance of distal cicatrix that could involve the lacrimal duct.

An additional consideration is the necessity of a nasoantral window in maxillary antrum surgery. The window is intended to improve postoperative drainage and help prevent mucocele formation. However, recent studies^{12,13} suggest that a nasoantral window may not be necessary.

Epiphora was a common complication in this series of orbital decompressions. This repre-

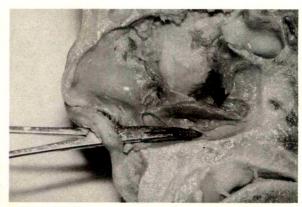


Fig. 3 (Seiff and Shorr). Placement of nasoantral window with hemostat on hemisected cadaver head. Arrow indicates elevated inferior turbinate.



Fig. 4 (Seiff and Shorr). Placement of nasoantral window with nasal rasp on hemisected cadaver head. Arrow indicates latex-filled nasolacrimal drainage system.

sents an important problem for patients with dysthyroid ophthalmopathy who already have multiple abnormalities of the ocular adnexa and accompanying symptoms. Great care must be taken to avoid nasolacrimal drainage system obstruction as a result of surgery. Future study is needed to develop more definitive ways of preventing this problem.

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Corneal Edema Related to Accidental Hibiclens Exposure

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Five patients developed corneal edema presumably caused by accidental preoperative ocular exposure to Hibiclens. In all cases, the patients complained of ocular pain after surgery. Conjunctival inflammation and corneal epithelial defects were found in all patients. Between two and ten weeks after exposure, stromal and epithelial edema, with a predilection for the inferior cornea initially, developed in all patients. The corneal edema resolved in three patients in approximately six months, leaving mild stromal scarring and reduced endothelial cell counts. The corneal edema in the other two patients progressed to diffuse bullous keratopathy, which eventually required penetrating keratoplasty. We recommend that Hibiclens be avoided in preoperative preparation of the facial skin to prevent accidental ocular exposure.

HIBICLENS, an antiseptic solution, has been available for use in the United States since 1976. Recent reports have suggested that ocular exposure to Hibiclens at the time of presurgical preparation of the facial skin may cause corneal toxicity. ¹⁴ Corneal involvement has ranged from transient epithelial defects that healed without sequelae^{2,4} to chronic corneal ulcers that led to corneal opacification. ¹ Herein we

describe five patients who developed corneal edema, a previously unemphasized complication of Hibiclens exposure.

Case Reports

Case 1

A 60-year-old woman underwent a facelift after administration of general anesthesia. The operative site was scrubbed with Hibiclens, aqueous Zephiran (1:750 benzalkonium chloride), and saline. When the patient awoke, she complained of severe pain and blurred vision in the right eye, which persisted for two weeks.

One week after surgery, best-corrected visual acuity was R.E.: 20/100 and L.E.: 20/30. The bulbar conjunctiva of the right eye was hyperemic and a large corneal epithelial defect was present. A regimen of polymyxin B sulfateneomycin sulfate-hydrocortisone ophthalmic ointment was started, and the epithelial defect healed within one week. Two weeks after surgery, a gray haziness of the stroma and punctate epithelial staining of the superotemporal cornea were noted. Because of photophobia and blurred vision, fluorometholone eyedrops every four hours were started.

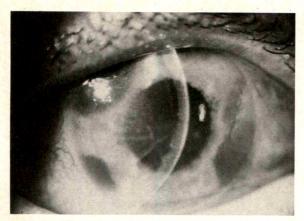
Two months later, uncorrected visual acuity was R.E.: 20/200 and L.E.: 20/20. The bulbar conjunctiva of the right eye was injected. The cornea of the right eye showed diffuse stromal and epithelial edema with inferior bullae. Vascular invasion of the cornea at the midstromal level was noted in the 5, 8, and 11 o'clock meridians with associated hemorrhages (Figure, left). Corneal sensation was reduced in the right eye. A mild aqueous flare without keratic precipitates was observed in the right eye. The left eye was normal. Intraocular pressure by applanation tonometry was 19 mm Hg in each eye. Both retinas were normal.

Herpes simplex titers by complement fixation were positive at 1:8. Fluorescent treponemal

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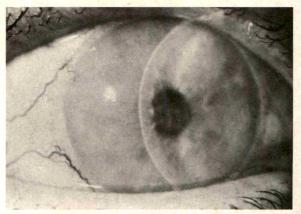


Figure (Phinney and associates). Case 1, right eye. Left, Intrastromal hemorrhages and diffuse stromal edema two months after facial surgery. Right, Clearing of intrastromal hemorrhages and diffuse bullous keratopathy one year after facial surgery.

antibody absorption, fluorescent antinuclear antibody, and rheumatoid factor were negative.

The patient was given topical prednisolone acetate 1% hourly, which was gradually tapered to one drop every other day over seven months. The intrastromal hemorrhages resolved. The bullous keratopathy gradually worsened, and her visual acuity progressively decreased to counting fingers (Figure, right).

One year after her facelift, the patient required a penetrating keratoplasty and extracapsular cataract extraction with posterior chamber intraocular lens implantation. Postoperatively, the corneal graft was clear, and uncorrected visual acuity improved to 20/50 within three months of surgery.

Histopathologic examination of the corneal specimen demonstrated an intact Bowman's layer and marked stromal scarring predominantly involving the posterior one third of the cornea. Descemet's membrane was lost in processing. Immunohistochemical stains for herpes simplex type 1 and type 2 were negative. Viral and bacterial cultures of the specimen were negative.

Case 2

A 45-year-old woman underwent the fourth revision of a cosmetic blepharoplasty. Two weeks before surgery, uncorrected visual acuity was R.E.: 20/25 and L.E.: 20/20. Schirmer tear volumes with anesthesia yielded 10 mm of wetting bilaterally after five minutes. The cornea of the right eye had a small nasal pterygium and inferior punctate staining with fluores-

cein, secondary to slight lagophthalmos. The left eye was normal.

At the time of blepharoplasty, the plastic surgeon used Hibiclens to prepare the skin. In the recovery room, the patient complained of severe bilateral ocular pain.

She was examined one week after surgery because of persistent ocular pain. Her right cornea had an oval area of epithelial punctate staining with fluorescein measuring approximately 4 × 7 mm. The left cornea had minimal punctate staining in the inferonasal quadrant. She had slight lagophthalmos and incomplete blinking in both eyes. She was treated with pressure patching of the right eye for one week.

Three weeks postoperatively, uncorrected visual acuity was R.E.: 20/400 and L.E.: 20/60. The cornea of the right eye showed diffuse bullous keratopathy. Stromal and epithelial edema were noted below the visual axis in the left eye. The patient was treated with topical 0.5% chloramphenicol eyedrops and 5% sodium chloride ointment.

Because of corneal stromal neovascularization, the patient was treated with topical prednisolone acetate 1% twice a day for two weeks. The bullous keratopathy resolved slowly and cleared seven months after surgery, at which time best-corrected visual acuity was 20/30 in each eye. Slit-lamp examination demonstrated central stromal scarring of the right cornea and a mild stromal haziness in the left cornea. Pachymetry of the central cornea measured 0.51 mm in the right eye and 0.55 mm in the left eye, with endothelial cell counts of 1,200 cells/mm² in the right eye and 1,000 cells/mm² in the

left eye. The endothelial cells in both eyes showed polymegathism.

Case 3

A 39-year-old woman underwent bilateral intraoral sagittal split osteotomy for advancement of her mandible to treat mandibular retrognathia. Hibiclens solution was used to prepare the face for surgery. After she awoke in the recovery room, her left eye was red and she experienced ocular discomfort, photophobia, and blurred vision.

Six days after surgery, visual acuity was L.E.: 20/80. The bulbar conjunctiva was edematous and a central corneal epithelial defect was present. Viral and bacterial cultures of the cornea yielded only *Staphylococcus epidermidis*. Results of examination of the right eye were normal. Cyclopentolate 1% and tobramycin eyedrops were instilled in the left eye and the eye was patched. The epithelial defect healed within three days. The patient was then treated with prednisolone acetate 1% eyedrops three times daily. Two weeks after surgery, the corneal stroma became diffusely edematous, with epithelial edema overlying the inferior half. Corneal sensation was absent in the left eye.

Two months after surgery, visual acuity was L.E.: counting fingers and the cornea appeared hazy, with an inferonasal pannus. An area of bulbar hyperemia and edema were present adjacent to the inferior corneoscleral limbus. She was treated with oral corticosteroids and topical antiviral agents. Three months after surgery, visual acuity had improved to 20/200. The left cornea showed less vascularization, but diffuse corneal edema remained. Enlarged corneal nerves were first observed five months after surgery. Six months after surgery, the bulbar conjunctival hyperemia and edema had improved, but her visual acuity and corneal edema remained unchanged. Slit-lamp examination of the endothelium by specular reflection demonstrated much larger and fewer cells in the left eye compared to the right eye. A corneal transplant was performed ten months after oral surgery. Histopathologic examination of the corneal button demonstrated changes consistent with bullous keratopathy, including an abnormal and attenuated endothelial cell layer.

Case 4

A 45-year-old man underwent a six-hour, left temporal craniotomy for removal of a meningioma. Hibiclens was used to prepare the skin preoperatively. A drop of Hibiclens was noted to go into the left eye, but the eye was not irrigated. In the recovery room, the patient complained of burning pain in the left eye. He was examined at the bedside four hours after surgery. A gray opacification of the inferior one third of the cornea was noted, with an epithelial defect overlying this area. Punctate staining of the central 4 mm of the cornea was also found. The eye was copiously irrigated and patched after application of erythromycin ophthalmic ointment.

Fourteen hours later, visual acuity was L.E.: 20/200. An epithelial defect over the inferior two thirds of the cornea was present. The stroma was mildly thickened but clear. The bulbar conjunctiva showed marked injection and edema but no ischemia. The anterior chamber had a mild cellular reaction.

After one more day of pressure patching, the appearance of the left eye was unchanged except that the defect was 50% healed and the visual acuity was 20/70. Two days later, visual acuity had improved to 20/25, the defect had healed, and the anterior chamber was quiet. One week later, the patient complained of a mild burning sensation and tearing. Slit-lamp examination demonstrated conjunctival injection, a mild haze of the inferior half of the cornea, midstromal vessels encroaching 1 mm into the inferior cornea, several pigmented keratic precipitates, and a quiet anterior chamber. He was treated with prednisolone acetate 1% eyedrops twice daily.

Two months postoperatively, the inferior half of the cornea had moderate stromal and epithelial edema, although the patient reported less burning and tearing. No corneal scarring was noted. There was no progression of the corneal vascularization. The anterior chamber was clear. Fluorometholone 1% eyedrops were prescribed for use hourly while awake. On examination one week later, the corneal edema had progressed to involve the superior cornea. However, the corneal edema slowly cleared over the following month. Four months after surgery, the endothelial cell count appeared reduced by specular reflection. Some discomfort and photophobia persisted.

Case 5

A 37-year-old woman underwent nasal septal surgery. The face was scrubbed preoperatively with Hibiclens, and the eyes were taped during surgery. The patient noted irritation of both eyes postoperatively, with the right eye affected more than the left. She was seen by an ophthalmologist one week later. Visual acuity

was R.E.: 20/30 and L.E.: 20/20. The cornea of the right eye showed diffuse punctate staining with fluorescein and peripheral epithelial edema. There was a rare cell in the anterior chamber. The left eye showed minimal punctate staining with fluorescein. The patient was given 0.1% dexamethasone phosphate eyedrops four times a day in the right eye and twice a day in the left eye. Within one week, the corticosteroid eyedrops were discontinued because the punctate keratopathy appeared to be clearing.

One month after surgery, best-corrected visual acuity was 20/20 in each eye. The patient still showed some mild inferior conjunctival injection, but the corneas were clear.

She returned ten weeks postoperatively because of the development of a red, photosensitive right eye with decreasing vision. She was found to have diffuse epithelial and stromal edema of the right cornea, which was more prominent inferiorly. There were some folds in Descemet's membrane and a minimal anterior chamber reaction. The patient was treated with prednisolone acetate 1% eyedrops every two to three hours.

Three months after surgery, the patient was referred for examination of the cornea. She was using one drop of prednisolone acetate 1% four times a day. Visual acuity was R.E.: 20/30 and L.E.: 20/20. The right eye showed some mild conjunctival injection. The corneal stroma had a diffuse haze, which was especially prominent at the level of the endothelium. The stroma was edematous inferiorly and there were rare keratic precipitates. The anterior chamber was clear. Corneal pachymetry measured 0.68 mm in the right eye. Results of slit-lamp examination of the left eye were normal. Dosage of the corticosteroid eyedrops was increased to once per hour and cycloplegics were instilled.

Four months after surgery, visual acuity was R.E.: 20/20-2 and L.E.: 20/20-1. Corneal pachymetry measurements were 0.54 mm on the right and 0.53 mm on the left. The right cornea showed mild stromal haziness inferiorly and an irregular endothelial mosaic. Over the next several weeks, the corticosteroid eyedrops were tapered. Although the patient's photophobia improved, she still noted some mild glare around lights.

Specular microscopy performed six months after surgery showed an endothelial cell count of 1,000 cells/mm² in the right eye and 2,200 cells/mm² in the left eye.

Seven months after surgery, best-corrected visual acuity was R.E.: 20/25 and L.E.: 20/20.

Slit-lamp examination of the right cornea showed a mild stromal haze, which was most prominent inferiorly. The endothelial mosaic appeared irregular with cornea guttata. There was a fine vascular pannus at the inferior corneoscleral limbus of the right eye. Results of the remainder of the examination were unremarkable.

Discussion

We observed corneal edema in six eyes of five patients who all underwent facial skin preparation with Hibiclens before surgery. In one case, accidental spillage into the eye was noted but ignored. In all cases, the patients complained of ocular pain after surgery. Conjunctival inflammation and corneal epithelial defects were found in all patients. Corneal edema was observed in all patients from two to ten weeks after exposure, with a predilection for the inferior cornea initially. The stromal and epithelial edema of four corneas of three patients gradually cleared within six to seven months, leaving mild stromal scarring and reduced endothelial cell counts. The corneal edema in two patients progressed to bullous keratopathy involving the entire cornea and eventually requiring penetrating keratoplasty. All patients developed corneal neovascularization. Two of the five patients were noted to have decreased corneal sensation. We observed thickened corneal nerves in one of our patients, but this finding has been described before in cases of bullous keratopathy and has been attributed to chronic and persistent irritation of the corneal nerves.⁵

Compared to previously reported cases, 1,2,4 our cases seem to fit into an intermediate category in the spectrum of ocular injury after exposure to Hibiclens. Hamed and associates1 described two cases of severe Hibiclens keratitis characterized by chronic epithelial defects, vascularization, opacification, thinning, and ectasia. Shore4 described two mild cases of Hibiclens corneal exposure in which he found postoperative epithelial defects that healed rapidly without sequelae. Stott² described a surgeon who accidentally splashed Hibiclens into his eye while scrubbing before surgery and was found to have multiple corneal epithelial defects and decreased visual acuity for one week. Our cases were less severe than those reported by Hamed and coworkers, but permanent visual impairment did result in two pa-

tients.

The cytotoxic effect of chlorhexidine, the active antiseptic agent in Hibiclens, is well recognized. In low concentrations, it has killed human epithelial cells and fibroblasts, and rat macrophages.6 Toxicity to corneal epithelium has been demonstrated in many studies.7-10 Hamill, Osato, and Wilhelmus11 found that chlorhexidine gluconate in 2% and 4% concentrations significantly reduced epithelial healing rates after a single 40-µl drop. Mac Rae, Brown, and Edelhauser¹⁰ found that a single 30-µl drop of Hibiclens caused sloughing of one epithelial cell layer 30 minutes after exposure and the entire epithelium three hours after exposure. Another study showed that total exfoliation of the upper epithelial cell layer resulted from exposure to 0.5% chlorhexidine.8 Hamed and associates1 showed nearly total absence of epithelium on rabbit corneas irrigated with Hibiclens for five or 15 minutes. Scanning electron microscopic studies of rabbit and cat corneas exposed to chlorhexidine have demonstrated epithelial loss of microvilli and wrinkling of plasma membranes, with disruption of contact between adjacent cells. 12

The corneal edema observed in our patients may be attributed to direct endothelial toxicity. Endothelial toxicity to chlorhexidine was demonstrated by Green and associates9 who found that rabbit endothelium swelled in vitro when perfused with chlorhexidine digluconate concentrations greater than 2%. In the study by Hamed and associates,1 the rabbit corneal endothelium showed attenuation and hydropic degeneration. In their study, a cornea irrigated for 15 minutes with Hibiclens was examined six weeks after exposure and, in addition to prominent stromal vascularization and scarring, showed endothelial replacement by a thick retrocorneal membrane. The histopathologic studies of the cornea obtained from our Case 3 and endothelial changes noted by specular microscopy in four of our cases support the cytotoxic effects of Hibiclens on the endothelium. The gradual progression of stromal and epithelial edema observed in our patients may be attributed to chronic exposure of the endothelium to chlorhexidine. This could be explained by a slow release of chlorhexidine bound to proteins in the corneal stroma. Green and associates9 found evidence of chlorhexidine binding to proteins in rabbit cornea.

The penetration of chlorhexidine, a cationic substance, into the corneal stroma may have been facilitated by the detergent in Hibiclens, which is a nonionic poloxamer¹³ and a member

of the family of inert surfactants known as Pluronic polyols. 14 Nonionic detergents have been found to be generally harmless to rabbit eyes, but Marsh and Maurice 15 found that single drops of certain nonionic detergents are capable of increasing corneal permeability to fluorescein, presumably via disruption of the surface epithelial barrier. Further, the severity of keratitis in Case 1 could possibly have been enhanced by simultaneous exposure to Zephiran (1:750 benzalkonium chloride). The concentration of benzalkonium chloride in this product far exceeds the amount that has been shown to cause corneal epithelial damage. 12,16

Hibiclens is an effective antiseptic cleanser that has been advocated for wide use, including preoperative skin preparation. 17-19 The combination of exposure to a high concentration of chlorhexidine, its ability to bind to proteins that slowly release it, and potential epithelial disruption by detergent probably all contribute to the toxic effects that have been observed after corneal exposure to Hibiclens. The manufacturer has issued a warning regarding ocular toxicity to the medical community. Ophthalmologists should alert their colleagues in other surgical specialties of the danger Hibiclens poses to the eye. Hibiclens should be replaced with less noxious agents such as povidoneiodine solution for preoperative preparation of the head. Further, inadvertent or accidental spillage of Hibiclens into the eye should be treated immediately with copious irrigation, and ophthalmic consultation should be requested.

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OPHTHALMIC MINIATURE
Aye, himself loves what does him good; but why?
'Gets good no otherwise. This blinded beast
Loves whoso places flesh-meat on his nose,
But, had he eyes, would want no help, but hate
Or love, just as it liked him: He hath eyes.

Robert Browing, "Caliban upon Setebos," 1864

Suramin Keratopathy

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Vortex keratopathy occurred in six patients given high-dose intravenous suramin for adrenocortical carcinoma. The corneal findings were bilateral and symmetric. Two patients complained of foreign-body sensation. One patient developed opacities of the anterior lens epithelium. Histopathologic studies of the eyes in one patient showed intraepithelial apical deposits in the cornea, conjunctiva, and lens epithelia. By electron microscopy, these deposits were found to be membranous lamellar inclusion bodies. These findings, as demonstrated by osmium-PAS staining and electron microscopy, were similar to those in other drug-induced lipid storage diseases.

Suramin was originally developed as an antitrypanosomal agent. It inhibits many lysosomal enzymes and induces systemic mucopolysaccharidosis in animals when given in high doses. There have been few reports of ocular toxicity in dosages used for parasitic infections. Recently, however, toxic keratopathy was reported in five AIDS patients treated with high-dose suramin. Three of these patients had vortex keratopathy and two had epithelial and subepithelial opacities. The total dose of suramin in these patients ranged from 3.2 to 17.2 g.

Herein we report the clinical findings of vortex keratopathy in six patients treated with high-dose intravenous suramin for adrenocortical carcinoma. The corneal findings were similar to those in Fabry's disease or the druginduced keratopathies of chloroquine, amiodarone, and chlorpromazine. The histopathologic, including osmium-PAS staining, and electron microscopic findings in one case are also described.

Patients and Methods

All patients (Table) were participants in a clinical trial conducted at the National Institutes of Health of high-dose intravenous suramin for the treatment of unresectable adrenocortical carcinoma. Each patient had a pretreatment ophthalmic examination, including visual acuity, color vision, slit-lamp biomicroscopy, tonometry, ophthalmoscopy with a dilated pupil, electroretinography, and electroculography. After initiation of treatment, each patient was seen weekly for measurement of visual acuity and slit-lamp biomicroscopy. Ophthalmoscopy with a dilated pupil, electroretinography, and electro-oculography were repeated at four to eight weeks.

Case Reports

Case 4

A 44-year-old man received suramin for adrenocortical carcinoma; results of the pretreatment ophthalmic examination were normal. After three weeks of treatment, the patient developed vortex keratopathy in both eyes. During the fifth week, he experienced pain and photophobia in the left eye. Corneal findings included vortex keratopathy and a superficial punctate keratopathy, as well as a concentric ring of partially eroded epithelium 3 mm from the corneoscleral limbus in the left eye. Treatment with topical lubricants resulted in resolu-

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TABLE PATIENT DATA

PATIENT NO., AGE (YRS), SEX	WEEKLY DOSE OF SURAMIN	SURAMIN SERUM LEVEL AT ONSET OF KERATOPATHY (µG/ML)	TOTAL DOSE AT ONSET OF KERATOPATHY (G)	CLINICAL FINDINGS
1, 27, F	1,400 mg/m ²	185	10.9	Vortex keratopathy and inferior superficial punctate kera- topathy in both eyes
2, 45, M	1,400 mg/m ² (3rd-wk dose not given)	200	10.2	Vortex keratopathy in both eyes
3, 31, F	1,400 mg/m ²	154	8.1	Vortex keratopathy in both eyes
4, 44, M	1,400 mg/m ² (3rd-wk	128	5.2	Vortex keratopathy in both eyes
	dose not given; 4th-wk dose, 800 mg/m ²)	170	9.0	Peripheral epithelial erosions in left eye
5, 28, F	1,400 mg/m ² (7th- and	169	9.8	Vortex keratopathy in both eyes
	8th-wk doses, 700 mg/m ²)	244	14.6	Diffuse superficial punctate keratopathy and conjunctival injection in both eyes
		164	15.8	Stellate pattern of opacities in anterior lens epithelium in both eyes
6, 31, F	1,400 mg/m ² every 4 days	150	5.6	Vortex keratopathy in both eyes

tion of both the erosions and the superficial punctate keratopathy.

Case 5

A 28-year-old woman with normal results on a pretreatment ophthalmic examination was first noted to have epithelial deposits on both corneas one day after her fourth dose of suramin. Over the next two weeks, the corneal epithelial pigmentation progressed and had the typical vortex appearance, similar to the other patients. After six weekly doses, the patient noticed foreign-body sensation and photophobia. On examination, conjunctival injection and superficial punctate keratopathy were noted as well as the vortex keratopathy. Her serum drug level was 244 µg/ml and the total dose was 14.6 g. Over the next two weeks, her dose was halved because of systemic side effects and her ocular symptoms resolved. At eight weeks, fine pigment opacities in a stellate configuration were noted in the anterior lens capsules of both eyes. Over the next several weeks, the vortex keratopathy and anterior lens capsule opacities became more prominent. Results of color vision, ophthalmoscopy, electroretinogram, and electro-oculogram testing remained normal. During week 22, the patient died of hepatic complications secondary to tumor extension. Her eyes were obtained for light and electron microscopy.

Histopathologic examination—The left eye was immediately opened. No gross abnormalities were observed. The cornea was sectioned. One portion was immediately embedded in O.C.T. compound and frozen at -70 C, and the other portion was fixed in glutaraldehyde for one hour, then transferred to formalin. After fixation, the eye was sectioned into three portions. One section underwent graded dehydration and methacrylate embedding of 2-µm sections for routine light microscopic examination, the second was exposed to osmium for one hour, then graded dehydration and methacrylate embedding of 2-µm sections for PAS staining was performed, and the third section underwent graded dehydration and was postfixed in osmium tetroxide and was then dehydrated and embedded in epoxy resin. Thin sections were stained with uranyl acetate and lead citrate for electron microscopic examination.

Results

All six patients receiving high-dose intravenous suramin developed a vortex epithelial keratopathy in both eyes. Initially, light golden deposits of the epithelium in the inferior one third of the cornea were seen. Progression to a darker brown pigmentation extending over the

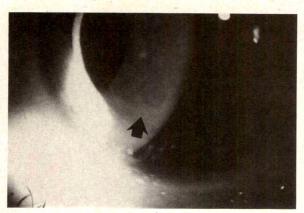


Fig. 1 (Holland and associates). Slit-lamp photograph demonstrating deposits in the corneal epithelium in a vortex pattern (arrow).

entire cornea in a whorl-like pattern occurred in all patients (Fig. 1).

Two patients complained of mild pain and photophobia. One of these patients (Patient 4) developed a concentric ring of partially eroded epithelium in the periphery of the left cornea. The other symptomatic patient (Patient 5) developed superficial punctate keratopathy. One other patient had clinical findings of superficial punctate keratopathy but was asymptomatic. Patient 5 also developed opacities of the anterior lens epithelium. This patient had the highest peak serum level of suramin, 244 µg/ml, which was obtained two weeks before the lens changes. The total dose of suramin in this patient at the onset of lens opacities was 15.8 g, which was 4.9 g higher than any other patient in the study. The earliest onset of vortex keratopathy was seen in Patient 4 who had a serum level of 129 μg/ml and a total dose of 5.2 g at the time the corneal changes were detected. The mean total dose at onset for all patients was 8.3 g.

In Patients 4 and 5, visual acuity decreased only while the epithelium was abnormal. Upon resolution of the irregular epithelium, vision returned to normal in both patients. Intraocular pressure remained normal in all cases. None of the patients had any visible retinopathy, and no changes in color vision, electroretinogram, or electro-oculogram were detected.

Histopathologic examination of the eyes from Patient 5 disclosed small clusters of particles in the paranuclear zone of the epithelial cells of the cornea (Fig. 2). These apical deposits were also seen in the perivascular and epi-

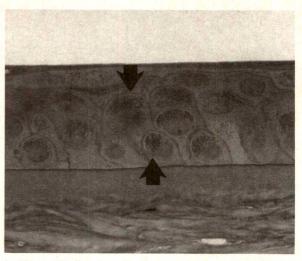


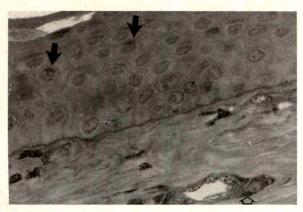
Fig. 2 (Holland and associates). Corneal epithelium with apical deposits (arrows) (osmium-PAS, \times 400).

thelial cells of the conjunctiva and lens epithelium (Fig. 3). These findings were best seen with osmium-PAS staining. Thickening of the basement membrane was noted in the retinal pigment epithelia at the fovea, but other retinal layers did not demonstrate any abnormalities. Small numbers of large cells (tumor cells) were seen in some choroidal vessels and stroma. Electron microscopic examination of the corneal and conjunctival epithelial cells showed numerous lamellar inclusion bodies measuring 0.1×0.25 µm, located mainly in the supranuclear zone of basal cells and wing cells (Fig. 4). Small numbers of lamellar inclusion bodies were also noted in the lens epithelium. The lens capsule had a multilaminar structure.

Discussion

Suramin has been used clinically since 1920 to treat trypanosomiasis and later to kill the adult onchocerciasis worm. It has recently been found to be an inhibitor of reverse transcriptase of the human immunodeficiency virus² and a trial of suramin to treat AIDS patients was instituted.

One of the effects of suramin is adrenal toxicity.³ Therefore, this medication has also been under trial as a new therapy for conditions of adrenal cortical hyperfunction, specifically



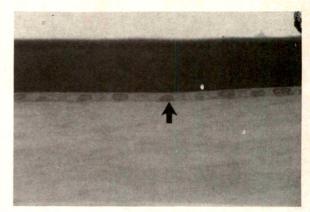


Fig. 3 (Holland and associates). Left, Conjunctiva with deposits seen in the epithelial (solid arrows) and perivascular (open arrow) cells. Right, Apical deposits seen in the lens epithelium (arrow) (left and right: osmium-PAS, × 400).

unresectable adrenocortical carcinoma. In the present study, six patients with adrenocortical carcinoma were treated with high-dose intravenous suramin. All patients had pretreatment ophthalmic examinations that showed no abnormalities; the patients were then examined weekly. Each patient developed bilateral vortex keratopathy similar to that seen in Fabry's disease and drug-induced lipid storage toxicity.

Three of the patients had additional findings of corneal epithelial toxicity: superficial punctate keratopathy in two patients and peripheral epithelial erosions in another. One patient developed stellate opacities of the anterior lens capsule. This patient had the highest serum level and total dose of suramin. None of the patients developed subepithelial opacities as was described in three of five patients with AIDS who were treated with suramin. Additionally, none of the patients in the AIDS study were reported to have superficial punctate keratopathy, corneal erosions, or lens opacities.

Side effects of suramin include nephrotoxicity, hepatotoxicity, pruritus, exfoliative dermatitis, arthralgias, and, rarely, anaphylaxis. 4.5 Ocular findings in patients with onchocerciasis and trypanosoma treated with intravenous and oral suramin include blepharitis, conjunctivitis, photophobia, and lacrimation. The corneal findings described in our study have not been reported in the patients treated with suramin for parasitic disease. One explanation is that the total dose of suramin was higher and the rate of peak serum drug level was faster in both the adrenocortical carcinoma and AIDS pa-

tients than is typically seen in the treatment of onchocerciasis or trypanosomiasis. Other patients receiving suramin might also develop

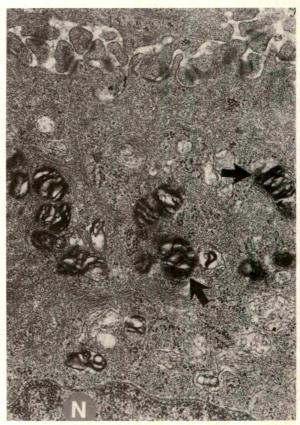


Fig. 4 (Holland and associates). Electron micrograph of corneal epithelium with lamellar inclusions (arrows) adjacent to the nucleus (N) (×28,000).

keratopathy and lens changes if the dose and rate of drug delivery were similar to that in our patients. Indeed, the severity of the keratopathy appeared to be related to the total dose in both the adrenocortical carcinoma and the AIDS patients treated with suramin.

Suramin binds strongly to proteins and is concentrated within lysosomes, probably as a result of endocytosis of the suramin-protein complexes.7 It causes glycosaminoglycan and sphingolipid accumulation when given intravenously to the rat. Histopathologically, the findings simulate a lipid storage disease.8 The histopathologic and electron microscopic findings in the corneas from Patient 5 appeared similar to those seen in drug-related vortex keratopathy and Fabry's disease. Methacrylate sections that have been PAS-stained after exposure to osmium demonstrate lipid deposition particles in the cornea, conjunctiva, and lens epithelia. These particles are lamellar inclusion bodies that have a lipid inclusion configuration in the cytoplasma. Similarly, electron microscopy of the cornea in patients taking chloroquine and amiodarone, and patients with Fabry's disease demonstrates lipid-bearing, concentrically arranged intralysosomal inclusions in the corneal epithelium.9

Although not detected clinically, amiodarone has been found to induce lamellar inclusion bodies in the choroid and retina. 10,11 In the present study clinical retinopathy was not detected. However, mild localized degeneration of the retinal pigment epithelium at the foveal zone was found histopathologically. As suramin is used more frequently, long-term follow-up examinations will be needed to evaluate possible retinal toxicity.

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Corneal Metastatic Calcification in Werner's Syndrome

I. Kremer, M.D., A. Ingber, M.D., and I. Ben-Sira, M.D.

We examined twin sisters with a clinical picture typical of Werner's syndrome. Both had undergone bilateral cataract extraction, one at 39 and one at 36 years of age, and had subsequently developed bilateral corneal metastatic calcification within a period of one to two years. In one twin, this keratopathy was associated with hypercalcemia. Each of the twins underwent penetrating keratoplasty in one eye, which was complicated by recurrence of metastatic calcification in a previously normal and clear corneal graft.

WERNER'S SYNDROME, typically characertized by a habitus of old age, atrophic dermatosis with trophic ulceration of legs, juvenile cataract, and endocrine disturbances, was first described by Werner in 1904.1 Other systemic and ocular features of this syndrome have since been described. 2-16 Werner's syndrome is a heredofamilial disorder characterized by premature graying of hair, premature baldness, short stature, gracile build, and "bird face."7-12 Generalized loss of the subcutaneous tissue and muscle mass^{2-4,13} and hypogonadism may occur in both sexes. 6,14,15 Some patients have generalized osteoporosis3,4 and diffuse metastatic calcification, particularly in the lower extremities, as well as calcification of blood vessels. Diabetes mellitus has also been described in young patients with Werner's syndrome.5,6

The ocular manifestations reported to date include retinitis pigmentosa-like features, ¹³ paramacular degeneration, ¹⁶ blue sclera, ² bullous keratopathy, and degenerative corneal changes after cataract surgery. ^{2,5,9,16} Herein we

describe another ocular manifestation of Werner's syndrome: metastatic corneal calcification developing after cataract extraction as well as penetrating keratoplasty.

Case Reports

Case 1

A 39-year-old woman was referred to our outpatient clinic because of bilateral mature cataract. Visual acuity was counting fingers at 1 m in both eyes and intraocular pressure was 18 mm Hg in each eye. The eyelids and anterior segments were normal. A mature cataract was present in both lenses, making visualization of the fundus impossible.

The general physical examination showed typical clinical features of Werner's syndrome including short stature; gray hair; and thin, wasted, tapering limbs, with the legs being affected more than the arms (Fig. 1). On histologic examination, skin changes consisted of loss of the subcutaneous tissue and sclerodermoid degeneration. Clinically, the skin was tightly adherent to the underlying tibia and ankle joint, and an indolent trophic ulcer was present over the lower right tibia. The patient had the characteristic placid, thin, bird face and looked much older than her age (Fig. 1). patient underwent uneventful bilateral intracapsular cataract extraction, after which her visual acuity improved to 20/26 with +12.0 diopters spherical correction in both eyes. Results of ophthalmoscopy were normal.

One year after cataract surgery the patient developed signs of subepithelial calcification in the lateral and medial peripheral zones of the cornea of her right eye in the area of the palpebral fissure. These changes became confluent over a 14-month period, after which time the entire corneal surface was covered by calcified white deposits located under the epithelium, resulting in a totally opaque right cornea (Fig. 2). Visual acuity had deteriorated to 20/200. Results of blood tests showed a slightly increased calcium level (12 mg/100 ml), a rela-

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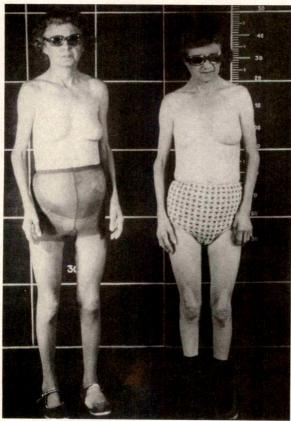


Fig. 1 (Kremer, Ingber, and Ben-Sira). Lett, Patient 2. Right, Patient 1. Note the typical clinical features of short stature, thin limbs, and bird face.

tively low inorganic phosphate level (2.3 mg/100 ml), a fasting blood sugar level of 140 mg/100 ml, and an abnormal glucose tolerance test.

She then developed recurrent corneal erosions in that same eye, which were treated by patching with antibiotic ointment. An attempt to remove the calcified deposits by superficial keratectomy combined with a solution of edetic acid failed. Several months later she underwent uneventful penetrating keratoplasty in her right eye. Three months later, the corneal graft was clear and visual acuity had improved to 20/26 with -2.5 cyl \times 130 correction. No disease was seen in the donor endothelium and no inflammation was present in the anterior chamber. Corneal thickness was normal. Histopathologic examination of the right corneal button showed large, subepithelial, calcified deposits associated with fibrous tissue that had replaced Bowman's layer. The calcified deposits extended deep into the corneal stroma,



Fig. 2 (Kremer, Ingber, and Ben-Sira). Patient 1. Note the total corneal opacity of her right eye (arrow) following cataract surgery.

which showed degenerative changes (Figs. 3 and 4). This finding of stromal calcification was compatible with the diagnosis of metastatic corneal calcification.

Two years later, signs of subepithelial calcification were noted in the medial and lateral pericentral zones of the corneal graft proper, in the area of the palpebral fissure. During the following year the calcified deposits became confluent throughout the entire donor cornea, rendering it totally opaque and reducing visual acuity to 20/200. Several attempts to remove the superficial calcified deposits by superficial keratectomy combined with local treatment with a solution of edetic acid failed to prevent the recurrence of this corneal degenerative process. Because of recurrence of the deposits in the corneal graft, we decided to delay the penetrating keratoplasty in that eye, although early signs of metastatic calcification were already present in the left cornea.

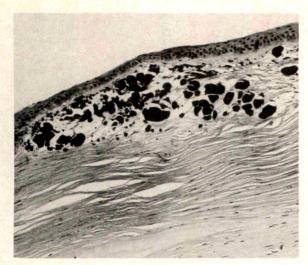


Fig. 3 (Kremer, Ingber, and Ben-Sira). Case 1. The histologic appearance of corneal metastatic calcification, consisting of large subepithelial calcified deposits associated with fibrous tissue replacing Bowman's layer. The calcified deposits extend deep into the corneal stroma, which shows degenerative changes (Von Kossa stain, ×125).

Case 2

This 36-year-old woman demonstrated almost the same features of Werner's syndrome as her twin sister (Patient 1). She had a placid, thin face and looked much older than her age (Fig. 1). She had sparse, gray hair and thin limbs, with severe atrophic changes in the subcutaneous and muscular tissues. She also had two indolent ulcers in the right ankle and one in the left. On histologic examination, the skin changes consisted of loss of the subcutaneous tissue and sclerodermoid changes.

Visual acuity was 20/130 in both eyes, intraocular pressure was normal, and the anterior segments were clear. Both lenses had a dense, progressive cataract, making visualization of the fundus difficult. At 36 years of age she underwent uneventful bilateral intracapsular cataract extraction, after which visual acuity improved to almost 20/20, with +13.0 diopters of spherical correction in both eyes. Results of ophthalmoscopy were normal.

Two years later she developed subepithelial metastatic calcification, which started in the lateral and medial peripheral zones of the cornea of her left eye. Results of blood tests showed normal calcium, inorganic phosphate, and glucose levels. Sixteen months later, the calcified deposits became confluent, affecting the entire corneal subepithelial area. This re-

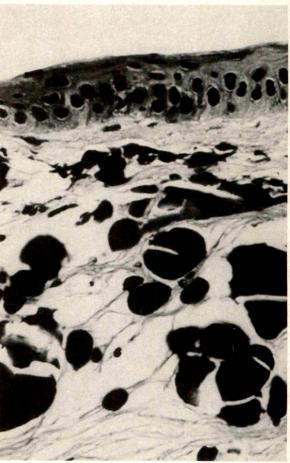


Fig. 4 (Kremer, Ingber, and Ben-Sira). Higher magnification of Figure 3 showing the subepithelial calcified deposits and fibrous tissue (Von Kossa stain, × 400).

sulted in total corneal opacification (Fig. 5), reducing visual acuity of the left eye to 20/200. Consequently, she underwent uneventful perforating keratoplasty in her left eye. Histologic examination of the corneal button showed metastatic corneal calcification (Fig. 6); the calcified deposits extended deep into the degenerated corneal stroma and were not confined to the subepithelial region, as is usually seen in band keratopathy. Four months after the operation the corneal graft was clear and visual acuity was close to 20/20 with -2.0 cyl \times 50 correction. One year later, evidence of metastatic calcification reappeared in the lateral and medial peripheral zones of the corneal graft in the area of the palpebral fissure. At this time, corneal graft thickness was normal, the appearance of the endothelial cells was normal, and there were no signs of uveitis. During the next two years

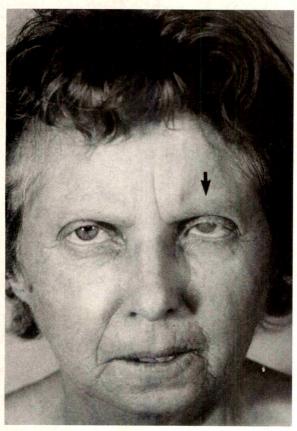


Fig. 5 (Kremer, Ingber, and Ben-Sira). Patient 2. Note the total corneal opacity of her left eye (arrow) following cataract surgery.

the graft became totally opaque as a result of diffuse calcific keratopathy. A repeat keratoplasty was not performed since visual acuity of the right eye was almost 20/20 with aphakic correction.

Discussion

Primary corneal degenerative changes have been known to occur in several hereditary skin disorders, including ectodermal dysplasia, ^{17,18} congenital ichthyosis, ¹⁹ keratosis palmaris and plantaris, ²⁰ Rothmund's syndrome, ^{2,21} pityriasis rubra pilaris, ²² and pachonychia congenita. ²³ The corneal changes in these disorders as well as those in Werner's syndrome ^{3,5,9,16} are usually attributed to the primary ectodermal defect. Calcific band keratopathy has also been observed in two successive generations ²⁴⁻²⁶ and in several distinct, genetically determined disor-

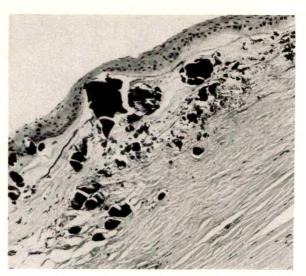


Fig. 6 (Kremer, Ingber, and Ben-Sira). Case 2. The histologic appearance of the left cornea showing the subepithelial calcified deposits and fibrous tissue replacing Bowman's layer. The calcified deposits extend deep into the corneal stroma, which shows degenerative changes (Von Kossa stain, ×125).

ders in which the keratopathy was probably primary and not associated with hypercalcemia (Norrie's disease,²⁷ X-linked recessive ocular dystrophy,²⁸ Hallerman-Doering syndrome,²⁹ and congenital band keratopathy³⁰).

Corneal disease in association with Werner's syndrome has been reported by several investigators. Ellison and Pugh⁵ noted a ground-glass appearance in the cornea of one patient, although they did not describe the changes in detail or discuss its origin. Oppenheimer and Kugel³ reported that one of their patients had recurrent attacks of keratitis, which was resistant to treatment, and eventually the entire cornea of one eye became opaque. They did not discuss the origin of the corneal disease or the histopathologic findings. Petrohelos¹⁶ described bullous keratopathy with secondary recurrent erosions and degenerative changes in patients with Werner's syndrome, which developed several years after cataract extraction. He concluded that cataract extraction in patients with this syndrome has a guarded prognosis because of possible postoperative complications such as bullous keratopathy, corneal ulceration, secondary glaucoma, and loss of vi-Bullous keratopathy as a late complication of cataract surgery in Werner's syndrome has been described in several reports.^{3,5,9,16,23,31-33} Rud⁹ reported that the cornea

in one patient with Werner's syndrome was covered by "thin calcareous crusts," which appears similar to a calcific keratopathy. Unfortunately, he did not study the biochemical or histologic nature of these crusts. This corneal complication was also found many years after intraocular surgery.

Our twin sisters showed a corneal complication of Werner's syndrome that has not yet been described or proven histologically. 1-16,31-33 The metastatic corneal calcification developed either after cataract extraction or after corneal transplantation of an otherwise normalappearing donor corneal button. It is not clear why the calcium deposition started in these women only after intraocular surgery. Nevertheless, that the diffuse calcific keratopathy occurred in both cases in a previously normal donor cornea points toward metastatic calcification as a possible mechanism for the calcium deposition in the two corneal grafts. It should be noted that metastatic calcification occurs in the presence of abnormal calcium or phosphate metabolism, 34-36 and neither cell necrosis nor tissue degeneration is present. Metastatic calcification of the skin, kidneys, and blood vessels has been described in patients with Werner's syndrome, probably as a result of hypercalcemia with hypophosphatemia caused by increased activity of the parathyroid glands.3,5 However, metastatic calcification has not been described in the cornea of patients with Werner's syndrome. Since the serum calcium level was found to be slightly above normal in only one of our patients, we postulate that the calcific keratopathy was only partially caused by a mechanism of metastatic calcification. It may well be that the primary ectodermal defect present in our patients also played an important role in the pathogenesis of their corneal disease through a mechanism of dystrophic calcification. Unfortunately, the patients refused to undergo tear collection and we could not measure calcium and phosphate levels in the tears. They were subsequently lost to follow-up.

We believe that the histopathologic findings in the corneas of our two patients support the diagnosis of metastatic corneal calcification and not that of calcific band keratopathy because of the large size of the calcified deposits, their deep location without any predilection for the subepithelial region, and the degenerative appearance of the corneal stroma.

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EDITORIAL

The Potential Use of Quinolones in Future Ocular Antimicrobial Therapy

Leonard R. Borrmann and Irving H. Leopold

For the past decade, the aminoglycosides, gentamicin and tobramycin, have been the therapy of choice for the treatment of ocular infections. The efficacy of these agents against a wide variety of gram-positive and gramnegative organisms has been verified in well-controlled clinical studies as well as in clinical practice. However, recent reports suggest that resistance to these antibiotics is increasing. Lorian and Atkinson³ reported that the number of aminoglycoside-resistant strains of systemic *Pseudomonas aeruginosa* had increased from 4% in 1971 to approximately 7% to 12% in

A similar increase in resistance has also been reported after topical administration of the aminoglycosides. As much as 8% to 10% of the ulcerative keratitis caused by *P. aeruginosa* may be resistant to aminoglycoside therapy. A Resistance appears to be even greater in ocular infections caused by gram-positive organisms. Because of the increasing incidence of

aminoglycoside-resistant microorganisms, research efforts have focused on the development of newer, more potent, anti-infective agents.

It is surprising that the quinolone antibiotics appear to be emerging as the next rising stars in antibiotic therapy. Nalidixic acid, the first quinolone, was approved for marketing in 1963. Although it is potent against various gram-negative organisms, its use has been limited because of the lack of therapeutic concentrations in serum and soft tissue.

In recent years, however, several new analogues of nalidixic acid, the fluoroquinolones, have shown broader activity ranges, greater intrinsic potency, and more enhanced tissue bioavailability than the parent compound. Currently, 18 of these analogues are under evaluation for systemic use and three are under study for ophthalmic use—ciprofloxacin, ofloxacin, and norfloxacin.

The fluoroquinolones exert their bactericidal effect by inhibiting the enzymatic activity of

DNA gyrase. This alters the structure and function of bacterial DNA. The new fluoroquinolones may also decrease the transfer of resistance between organisms by directly interfering with chromosomal DNA.⁶

In general, the quinolones exhibit greater in vitro potency compared to commercially available antibiotics against a wide spectrum of gram-positive and gram-negative organisms. The quinolones even appear to be effective both in vitro and in vivo against *Chlamydia trachomatic* ^{7,8}

Extensive research has been conducted to identify the in vitro potency of ofloxacin and norfloxacin against *P. aeruginosa*, *Staphylococcus aureus*, *S. epidermidis*, and *Streptococcus pneumoniae* isolated from ocular infections. Both ofloxacin and norfloxacin were equal to or more potent than commercially available topical antibiotics against *P. aeruginosa*. Ofloxacin was also two to 32 times more potent than norfloxacin, gentamicin, tobramycin, and chloramphenicol against *Staphylococcus* and *Streptococcus* species. 9,10

Data characterizing the in vitro activity of ciprofloxacin against ocular isolates are not currently available. However, the results of in vitro evaluations with systemic organisms indicate that its potency is equal to ofloxacin against gram-positive and most gram-negative organisms, and slightly more potent than ofloxacin against P. aeruginosa (S. Chartrand, International Congress of Antimicrobials and Chemotherapeutics, Oct. 4, 1987). After oral administration, ciprofloxacin is not absorbed into the systemic circulation or into the aqueous humor as rapidly or to the same extent as ofloxacin. Ofloxacin achieves a peak aqueous humor concentration that is several times higher than that of ciprofloxacin and attains high drug concentration levels in most tissues and body fluids. 11-13

Organisms resistant to the fluoroquinolones have been created under laboratory conditions. However, it is a difficult process, requiring two independent chromosomal mutations. When quinolone-resistant mutants occur, they are extremely sensitive to temperature and are slow growing. They display stringent nutritional requirements and readily revert back to quinolone-sensitive organisms. Thus, resistant organisms are unlikely to compete effectively with quinolone-sensitive organisms in a mixed environment. ¹⁴

Published results of the clinical efficacy of topical quinolones in humans are limited. Ofloxacin 0.3% eyedrops reportedly decreased the clinical signs of infection and eradicated the organism in 98% of the 325 cases of external ocular infections treated, including 92% of the patients with corneal ulcers. 15-17

Fortunately, few side effects have been reported with the use of topical quinolones. Of-loxacin is the only topical quinolone agent with available clinical trial information. In clinical studies, only six of 874 patients (0.69%) treated with topical ofloxacin eyedrops reported adverse events resulting from ofloxacin therapy. This compares favorably with the adverse event rate (5% to 10%) associated with topical aminoglycosides. 1,20

As a class, systemic quinolones are contraindicated in children, based on the results of animal studies. In immature dogs, quinolones were found to induce alterations in joint cartilage. Additional animal research with topical formulations is necessary before the safety of ophthalmic quinolones can be evaluated in children.

This overview suggests that topical quinolones may play a significant role in the future management of ocular infectious disease. In our era of cost containment, the quinolones may help hasten the cure and improve the cost effectiveness of antibiotic therapy. They may also provide the practitioner with a more effective tool to manage difficult-to-treat ocular infections. We await additional data on the effectiveness of these compounds to assess accurately their role in the future of ocular antimicrobial therapy.

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LETTERS TO THE JOURNAL

A Molecule Resembling Fibroblast Growth Factor in Aqueous Humor

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We have identified a polypeptide of approximate molecular weight 17 kD in 20 samples of normal human aqueous humor. On sodium dodecyl sulfate-polyacrylamide gel electrophoresis, this polypeptide comigrated with purified, pituitary-derived basic fibroblast growth factor. On Western blot analysis (Figure), the polypeptide reacted immunologically with a polyclonal antiserum raised against the biologically active fragment of basic fibroblast growth factor prepared from bovine brain tissue. We obtained the samples of aqueous humor by paracentesis of the anterior chamber after making the partial thickness limbal incision that is customary for cataract extraction. We used a 30-gauge needle and did not touch the corneal endothelium, iris, or lens. The subjects, who were undergoing elective cataract surgery, ranged in age from 60 to 90 years.

Reports have been published concerning the biologic effects of acidic and basic fibroblast growth factors. 1,2 It has been proposed that endothelial-cell growth factors, tumor angio-

genic factors, retina-derived growth factors, and eye-derived growth factors may be identical or homologous to acidic or basic fibroblast growth factor because of their high affinities for heparin and their capacity to stimulate the growth of cell types derived mostly, but not exclusively, from the first and second mesenchyme.¹

Previous work has focused primarily on the stimulatory or inhibitory activity of unfractionated aqueous humor, without identification of specific factors. However, the importance attached to the identification of specific growth factors in the aqueous humor is well merited. We believe that the consistent presence in vivo of a molecule in the aqueous humor that is indistinguishable from basic fibroblast growth factor is significant for several reasons. Such a growth factor has potential application to harvesting and propagation in vitro of those cells that are nourished normally in vivo almost exclusively by aqueous humor, such as lens epithelium, corneal endothelium, anterior iris stroma, and cells of the trabecular meshwork and Schlemm's canal system. Identification of a specific growth factor may help determine the pathogenesis of anterior segment abnormalities that are associated with disorders of cell growth, such as primary open-angle glaucoma.3 Identification of this molecule is also relevant to fibroblast proliferation4 and new vessel formation⁵ in Tenon's capsule at the site of surgical fistulas that eventually contribute to the failure of the surgical procedure. This fibroblast growth factor may also be significant in a condition such as neovascular glaucoma, an intractable disease in which new blood vessels

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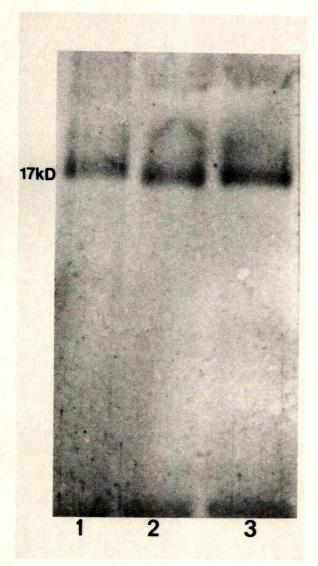


Figure (Tripathi and associates). Immunoblot showing binding of a polyclonal anti-basic fibroblast growth factor-antiserum to electrophoresed aqueous proteins sodium dodecyl sulfatepolyacrylamide gel electrophoresis on 27% weight/ volume total acrylamide. The samples of aqueous humor were obtained from human subjects aged 73 years and 87 years (lanes 1 and 2, respectively). Lane 3 contains purified bovine pituitary-derived basic fibroblast growth factor that had been isolated by using a heparin affinity column. The single band at 17 kD in each of the three lanes reacted immunologically with the basic fibroblast growth factor antiserum. Staining was done using an indirect peroxidase method.

and fibrocytic cells proliferate in the angle of the anterior chamber and on the surface of the iris. Our finding opens up the possibility of using a fibroblast growth factor-neutralizing antibody or a molecule resembling fibroblast growth factor as a new therapeutic modality, depending on the nature of the disorder.

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Optic Disk Neovascularization and Rubeosis Iridis After Surgical Resection of the Optic Nerve

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The association between ocular ischemia and neovascularization has been well documented. We treated a patient who developed optic disk neovascularization and rubeosis iridis after surgical resection of the optic nerve.

A 45-year-old woman complained of decreased vision in the left eye and was found to have massive swelling of the optic disk. Visual

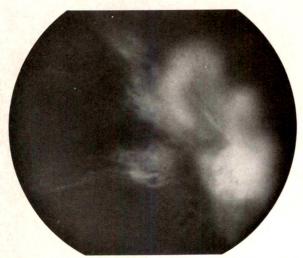


Fig. 1 (Bovino, Marcus, and Nelsen). Choroidal flush phase of the fluorescein angiogram shows optic disk neovascularization extending toward the peripapillary retina.

acuity in the left eye was 20/200, but deteriorated rapidly to no light perception. The right eye was normal. Results of medical examination were normal. Computed tomography showed massive swelling of the optic nerve. A neurosurgical exploration of the optic nerve through a frontal approach was performed. A biopsy was done and the frozen section was found to be malignant. The entire optic nerve from the optic foramen to the posterior aspect of the globe was resected surgically. Definitive pathologic evaluation disclosed nonspecific optic neuritis.

Three months after surgery the patient developed optic disk neovascularization and rubeosis iridis with neovascular glaucoma. A fluorescein angiogram documented the growth of new vessels on the surface of the disk, which filled during the choroidal flush phase of the angiogram (Fig. 1) and stained in the late phases (Fig. 2).

The optic nerve head receives a dual blood supply from retinal circulation and posterior ciliary circulation.² The lamina cribrosa and the prelaminar and retrolaminar regions derive much of their blood supply from posterior ciliary circulation, either through the posterior ciliary arteries, Zinn's vascular circle, Haller's circle, or the peripapillary choroid, while the surface nerve fiber layer is supplied mainly by normal branches of the retinal arterioles. Using rapid sequence fluorescein angiography, Asdourian, Goldberg, and Busse⁸ showed that optic disk neovascularization can develop in diabetics solely from the choroidal circulation.

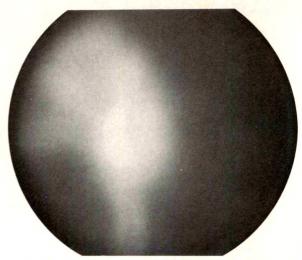


Fig. 2 (Bovino, Marcus, and Nelsen). Late phase of the fluorescein angiogram shows hyperfluorescence and staining of the neovascular tissue.

The development of neovascularization in our patient, after total resection of the optic nerve and central retinal artery, provides anatomic correlation supporting this concept.

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Neodymium: YAG Laser for the Treatment of Encapsulated Blebs After Filtration Surgery

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The neodymium: YAG laser has been used to open blocked membranes obstructing the internal opening of filtration fistulas. 1,2 We used the

Nd:YAG laser successfully to reestablish filtration in a patient with an encapsulated Tenon's cyst three months after standard trabeculectomy.

A 57-year-old man was referred after pharmacologic mydriasis precipitated acute angleclosure glaucoma in both eyes. The intraocular pressures were 58 mm Hg in the right eye and 50 mm Hg in the left eye. After successful medical treatment, peripheral iridotomies were performed in each eye with both the argon blue-green and Nd:YAG lasers. Postlaser gonioscopy showed the angles to be open in both eyes. The patient was treated with maximal medical therapy, including timolol, pilocarpine, and acetazolamide, and his intraocular pressures were 33 mm Hg in the right eye and 17 mm Hg in the left eye. Visual acuity was 20/20 in both eyes. The visual field was normal in the left eye but a small central island remained in the right eye. After argon laser trabeculoplasty did not lower the intraocular pressure, an uncomplicated trabeculectomy was performed on the right eye.

The postoperative intraocular pressure remained at 4 mm Hg until the third postoperative week, when a large Tenon's capsule cyst was noted and the intraocular pressure increased to 29 mm Hg. The pressure decreased to 22 mm Hg after digital ocular massage. Despite extensive home digital ocular massage, the intraocular pressure remained at 23 mm Hg with maximal medications. Gonioscopy showed the filtration stoma site was open.

We used the Nd:YAG laser to open the cyst externally by aiming the beam directly at Tenon's capsule (Fig. 1). We did not use a contact lens. Care was taken to find an area near the periphery of the bleb where the conjunctiva was separated from Tenon's capsule in order to

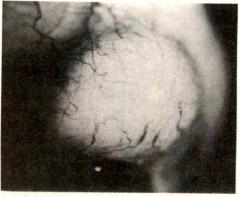


Fig. 1 (Ofner and Smith). Encapsulated bleb before Nd:YAG laser treatment.

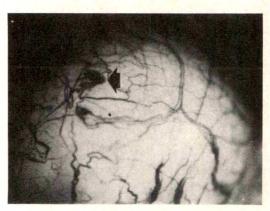


Fig. 2 (Ofner and Smith). Encapsulated bleb immediately after Nd:YAG laser treatment. Note the small, subconjunctival hemorrhage at the treatment site (arrow).

avoid inadvertent perforation of the conjunctiva. A total of three shots using 3.0-mJ power was used. Postoperatively, the pressure was 14 mm Hg, which decreased to 8 mm Hg after digital ocular massage. During the next two weeks, the pressure was between 6 and 8 mm Hg as acetazolamide and pilocarpine were stopped. The intraocular pressure has remained at 12 mm Hg while the patient has been taking timolol 0.5% only. We have not noted any complications from the procedure other than a small subconjunctival hemorrhage that subsequently resolved (Fig. 2).

The standard treatment for encapsulated filtration blebs has been massage, needling procedures, or surgical removal of Tenon's capsule.3,4 We describe a technique which may provide an alternative to the management of a Tenon's capsule cyst. Although it is possible this patient would have improved spontaneously, the time course of the pressure control and the improved appearance of the bleb suggest that the laser was effective in reestablishing filtration. We stress, however, that conservative treatments with digital massage and observation are usually the first approach.5 Also, care must be taken to treat an area where the conjunctiva is separated from Tenon's capsule in order to avoid perforation of the conjunctiva. If a safe site cannot be identified, it may be better to proceed with the more traditional surgical intervention.

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Recurrent Nanophthalmic Uveal Effusion Syndrome Following Laser Trabeculoplasty

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The danger of intraocular surgery in nanophthalmic eyes has been reported. 1,2 These eyes are prone to narrow angle glaucoma, necessitating iridectomy or iridotomy. Laser iridotomies are the treatment of choice in nanophthalmos, but recent reports suggest that uveal effusions are a potential complication of this form of therapy in nanophthalmic eyes. 23 We studied a case of recurrent uveal effusion following laser trabeculoplasty in a nanophthalmic eye.

A 62-year-old man was referred because of a sudden decrease of vision in his left eye. Visual acuity in the right eye was 20/60 with +11.00 refraction. An early cataract and a shallow peripheral choroidal detachment were noted. Visual acuity in the left eye was 20/200 with +11.00 refraction. A 360-degree ciliary body and choroidal detachment were noted, with inferior subretinal fluid extending through the macula (Fig. 1).

Nanophthalmic uveal effusion syndrome was diagnosed. Because of a decrease in visual acuity to counting fingers, an increase in sub-

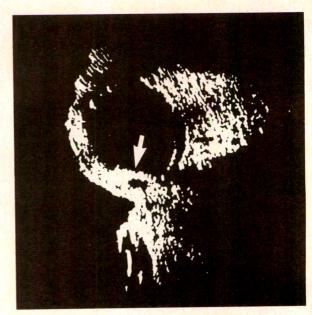


Fig. 1 (Good and Stern). Preoperative B scan. Arrow points to choroidal detachment.

retinal fluid, and failure to improve with systemic corticosteroids, surgery was performed using lamellar sclerectomies combined with sclerostomies in four quadrants at the equator in the left eye. The sclerectomies were triangular and measured 5 mm on each side. Circular sclerostomies of 1 mm were created in the center of each partial thickness sclerectomy with a Gass scleral punch. One month postoperatively, the uveal effusion and retinal detachment in the left eye had resolved and visual acuity had improved to L.E.: 20/80.

Six months later, the patient underwent argon laser trabeculoplasty in the left eye for sustained increased intraocular pressures that were not well controlled with medication. Treatment consisted of 70 burns applied to the superior 180 degrees of the trabecular meshwork using a spot size of 50 µm, a duration of 0.2 second, and an intensity of 1,100 mW. One week later the patient developed choroidal effusions and a serous retinal detachment in his left eye. Visual acuity was R.E.: 20/60 and L.E.: 20/400.

The serous retinal detachment in the left eye failed to resolve during the next three months, and the four-quadrant sclerectomy combined with sclerostomy procedure was repeated. Four new triangular sclerectomy/sclerotomy sites were dissected adjacent to the previous sclerectomies because of the difficulty in uncovering the previously dissected sclerectomies. Both

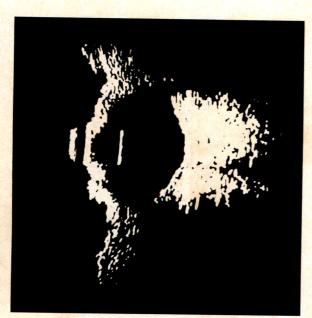


Fig. 2 (Good and Stern). Left eye after a second sclerectomy and sclerostomy procedure. The choroidal detachment has resolved.

the retinal and choroidal detachments resolved over a one-month period, and the patient's visual acuity improved to L.E.: 20/60 with no evidence of recurrence of uveal effusion or retinal detachment (Fig. 2). The retina has remained attached with no evidence of a recurrent uveal effusion during the last two years.

When nanophthalmic uveal effusion occurs, we advocate the use of sclerectomy surgery combined with sclerostomy as described by Gass and Jallow.4 Combined sclerectomy and sclerostomy surgery provides an outflow path for suprachoroidal fluid that apparently has difficulty exiting through the thickened sclera.5 If a second operation is necessary, it may be difficult to redissect the same areas. Nonetheless, Gass and Anderson (oral communication, 1987) have removed successfully the fibrous capsule from previous sclerectomy combined with sclerotomy sites with resolution of the uveal effusion. Small sclerectomies, which were used in our case, offer the surgeon the flexibility of repeating the surgical procedure in new sites on a previously operated on eye.

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Lacrimal Anomalies in Brachmann-de Lange's Syndrome

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Brachmann-de Lange's syndrome is characterized by microbrachycephaly, variable musculoskeletal manifestations with limb defects, mental retardation, growth failure, and a typical facies with anteverted nares, long philtrum, thin upper lip, and hirsutism. It may represent a genetically determined disorder, possibly autosomal dominant.

We studied a case of Brachmann-de Lange's syndrome with bilateral atresia of the ostium lacrimale and absence of the upper lacrimal canaliculi and puncta.

A 3-year-old boy with Brachmann-de Lange's syndrome was referred for evaluation of epiphora. He had had a birth weight of 1.2 kg. Initial medical treatment for congenital bilateral epiphora was unsuccessful, and he underwent probing at 2 years of age. A cleft palate was also repaired at 2 years of age. The patient displayed growth deficiency. Family history was noncontributory for epiphora or Brachmann-de Lange's syndrome.

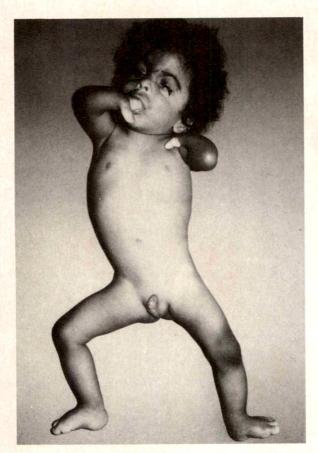


Fig. 1 (Aguirre Vila-Coro and associates). Clinical appearance of patient. Note long eyelashes, synophrys, hirsutism, upturned nose, long philtrum, and thin upper lip.

Results of examination disclosed microbrawith the facies typical of chycephaly Brachmann-de Lange's syndrome (Fig. 1), small genitalia, monodactyly of the right hand and ectrodactyly of the left hand, incomplete extension at both elbows, an antecubital pterygium on the right arm, and bilateral 2, 3 syndactylya of the toes. Karyotype was normal. Ophthalmologic findings included synophrys, long eyelashes, myopia of -11.50 diopters in the right eye and -14.50 diopters in the left, and a Mittendorf's dot in each lens. There was bilateral lacrimonasal duct obstruction and bilateral absence of the upper lacrimal punctum. No other ocular abnormalities were found.

Microsurgery failed to show upper lacrimal canaliculi, and the patient was treated with bilateral monocanalicular lacrimonasal intubation.² The tubes were removed five months later, and the patient has remained free of epiphora and discharge. Digital subtraction



Fig. 2 (Aguirre Vila-Coro and associates). Digital subtraction macrodacryoradiography of the right lacrimal passage. Note absence of the upper lacrimal canaliculus (arrow).

macrodacryoradiography, performed at the time of tube removal, showed small lacrimal sacs and confirmed the absence of upper lacrimal canaliculi (Fig. 2). The left lacrimonasal duct had a localized stenosis, and both lacrimonasal ducts were patent.

Long eyelashes, synophrys, and severe myopia are frequent ocular findings in Brachmann-de Lange's syndrome. Major manifestations of the disease include growth deficiency, mental retardation, microbrachycephaly, and a typical facies. Facial clefting and cardiac defects are variable features. The musculoskeletal manifestations range from small hands and feet to overt reduction in limb length. Though severe cases may be recognized readily, there is variability in the clinical manifestations.

Although congenital impatency of the lacrimonasal duct is frequent, bilateral absence of the lacrimal canaliculi and puncta is rare, and often represents an autosomal dominant trait.³ However, the association of two separate dominant mutations is much less likely than there being a single cause for Brachmann-de Lange's syndrome and the lacrimal anomalies. Absent upper lacrimal puncta and canaliculi may be asymptomatic and may be overlooked unless an associated problem causes epiphora, warranting careful lacrimal evaluation.

Our findings suggest that an evaluation for lacrimal anomalies should be a part of the

routine assessment proposed for patients with Brachmann-de Lange's syndrome.¹

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Recurrent Lacrimal Abscess Caused by Eikenella corrodens

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Eikenella corrodens is a slow-growing, facultative, anaerobic, gram-negative bacillus that forms part of the normal flora of the mouth, nasopharynx, bowel, and urogenital tract.¹ Its pathogenicity in humans has only recently been recognized.² In 1979, Schwartz and associates³ reported two cases of orbital cellulitis caused by E. corrodens. Recently, Stoloff and Gillies⁴ analyzed 33 cases of E. corrodens infection in a general hospital and found two cases of conjunctivitis and one of dacryocystitis. We report a case of recurrent lacrimal abscess caused by E. corrodens to emphasize the potential of this organism to cause ocular adnexal infections.

A 26-year-old man was involved in a traffic accident in June 1984. He sustained several severe injuries including a fractured middle third of his face with a ruptured right globe and a posteriorly displaced left globe. During the early period of recovery he had two episodes of meningitis, which responded to chlorampheni-

col and metronidazole therapy. Repeated cerebrospinal fluid cultures did not show any pathogens. In April 1985, he developed a painful swelling at the inner canthus of the left eye. A lacrimal abscess was diagnosed. The abscess was drained surgically, and the patient was treated with a one-week course of 250 mg of oral ampicillin and 250 mg of floxacillin. Aerobic culture of the pus showed Staphylococcus aureus. Between April 1985 and February 1986 he had three recurrences of the abscess, which were treated similarly with a favorable response each time. Apart from a scanty growth of S. epidermidis on one occasion, no organisms could be identified. In February 1986 the abscess recurred for the fifth time. In view of the gross disruption of the anatomic landmarks, magnetic resonance imaging was performed to determine the extent of the abscess (Fig. 1) before surgical excision. Prolonged anaerobic culture of excised material from the abscess disclosed E. corrodens and aerobically, a scanty growth of Haemophilus influenzae was also obtained. Histologic studies of the abscess showed a lining of stratified squamous to columnar epithelium, which was ulcerated at places. The wall was thickened and showed infiltration by chronic inflammatory cells and organized granulation tissue (Fig. 2). The patient has been followed up for 20 months without any recurrence of infection.

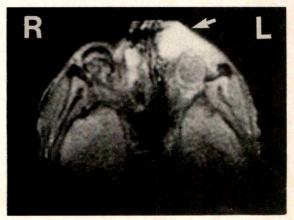


Fig. 1 (Dua and associates). A magnetic resonance image scan of the orbits. The T1-weighted image shows disorganized orbits. The right globe is disrupted and the outline of the artificial eye shell is clearly visible. The left globe is phthisical and posteriorly displaced. Note the abscess anteromedial to the eyeball and the circumscribed dense shadow (arrow), partly extending into the left nasal cavity.



Fig. 2 (Dua and associates). Histologic section of the lacrimal abscess (hematoxylin and eosin, \times 40). Note the ulcer (arrow) and the dense infiltration with chronic inflammatory cells.

To determine whether E. corrodens occurs as a commensal in the conjunctival sac, we obtained conjunctival swabs from the right eyes of 40 healthy volunteers. The test subject population consisted of 25 women and 15 men who ranged in age from 21 to 75 years. The conjunctival swabs were inoculated onto blood agar plates supplemented with clindamycin (5 mg/ml). The plates were incubated in 10% carbon dioxide at 37 C for 72 hours and then examined for the presence of E. corrodens. None of the swabs taken from the conjunctival sacs of the volunteers showed E. corrodens. Since E. corrodens does not form part of the normal conjunctival flora, it is likely that ocular adnexal infection such as dacryocystitis and conjunctivitis originates from the paranasal sinuses or nasopharynx. This is supported in our case in that the sinus walls were disrupted by trauma. The potential of E. corrodens to cause ocular infections, particularly recurrent dacryocystitis, needs to be recognized. The organism can easily be missed on routine cultures. It grows slowly and often requires more than 72 hours in an atmosphere of 5% to 15% carbon dioxide to grow. It can also be overgrown readily by other organisms. In our patient, the organism was probably not isolated during the early episodes because of either a failure to carry out anaerobic cultures or an inadequate duration of culture. Complete excision of the abscess prevented recurrent infection by this organism by removing the nidus of chronic focal inflammation which would normally favor its growth. Different strains of the organism are susceptible to most antibiotics such as ampicillin, cephalothin sodium, chloramphenicol, erythromycin, neomycin, penicillin, gentamicin, and vancomycin hydrochloride. This suggests that once recognized, the condition responds well to treatment.

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Correspondence

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The Risk of Cytomegalovirus Transmission by Penetrating Keratoplasty

EDITOR:

In the article "The risk of cytomegalovirus transmission by penetrating keratoplasty" by E. J. Holland, S. R. Bennett, R. Brannian, J. C. Osborne, J. A. Goeken, and J. H. Krachmer (Am. J. Ophthalmol. 105:357, April 1988), the authors conclude that the risk of cytomegalovirus transmission by corneal

transplantation appears to be low. I concur with this conclusion but not for the reasons given in their article. In immunocompromised patients, cytomegalovirus can be hematogeneously transmitted to the eye, frequently infecting the retina, the cells traversing the choroid, and the cells within the iris stroma. Cytomegalovirus has never been documented in central corneal tissue despite repeated attempts at isolation in tissue culture, immunocytologic staining, and in situ hybridization, even in inflamed eyes with extensive cytomegalovirus retinopathy. This makes the transmission of cytomegalovirus from a corneal donor by penetrating keratoplasty seem

almost a moot point.

One must question the underlying premise of any study based upon the analysis of IgG antibodies against cytomegalovirus in a corneal transplant recipient's serum as the sole determinant of whether cytomegalovirus has been transmitted either to intraocular structures, the ocular adnexa, or systemically to extraocular sites. There are several reports of cytomegalovirus retinopathy in which results of serologic studies for cytomegalovirus antibodies either remained completely negative throughout1 or fluctuated in a random fashion as compared to the intraocular disease process.2 Similarly, Culbertson and associates3 described two nonimmunocompromised patients with the acute retinal necrosis syndrome. Although varicella zoster was demonstrated in retinal tissue, results of serologic studies were nondiagnostic of varicella zoster. These results illustrate that intraocular infection with members of the herpesvirus family cannot be diagnosed reliably by studying serum. Although it is possible that systemic dissemination of cytomegalovirus from a corneal graft could be serologically detected, the pattern of serologic response to this ubiquitous virus may fluctuate throughout life, just as antibody levels to herpes simplex may fluctuate and not correlate with reactivation from its latent state. For this reason, the additional determination of IgM antibodies against cytomegalovirus would provide corroborative evidence of true seroconversion in the transplant recipients' sera, and the IgM status in the donors' sera would also be of interest to determine whether the cytomegalovirus infection was acute.

Most cytomegalovirus infections in nonimmunocompromised hosts are asymptomatic and subclinical. Patients may harbor or be in-

fected with more than one strain of cytomegalovirus. These clinical isolates can be differentiated by restriction enzyme analysis, which serves as a fingerprint of the virus. Without performing sophisticated studies such as these, however, it is not possible to determine if a patient was infected with a strain of cytomegalovirus from the donor graft, as opposed to being infected with an exogenous strain of this ubiquitous herpesvirus around the time

of penetrating keratoplasty.

For the reasons listed, the value of the authors' study appears to be limited. I would stress that the viral characteristics described above are specific to cytomegalovirus. They are not shared by human immunodeficiency virus, which causes a productive infection throughout the life of the individual along with a humoral immune response, or hepatitis B virus, which leads to shedding of an enormous antigen load followed by an immune response and may lead to persistent infection. The authors' assertion that this study of transmission of cytomegalovirus by penetrating keratoplasty will throw light on the transmission of human immunodeficiency virus (or hepatitis virus) is not consistent with what is known about infection and immunity with these other viral agents.

> JAY S. PEPOSE, M.D. St. Louis, Missouri

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Reply _

EDITOR:

The purpose of our study was to determine the risk of cytomegalovirus transmission by penetrating keratoplasty. This question is im-

portant for two reasons. First, although the Eye Bank Association of America has no official recommendation regarding donors who test positive serologically for cytomegalovirus, some of those corneas are not being used for transplantation. If the risk of transmitting the virus by penetrating keratoplasty is minimal, potentially good corneal tissue is being wasted. Secondly, if the possibility of transmission is not minimal, immunocompromised patients who undergo penetrating keratoplasty (including those taking immunosuppressive drugs for ocular or systemic conditions and those with malignancies) may be at risk, because cytomegalovirus infection in such a patient is much more likely to result in clinical disease. In some cases, the clinical manifestations of a cytomegalovirus infection can lead to disseminated infection and even death.1

Although cytomegalovirus has not been detected in central corneal tissue, this is not proof that it cannot be transmitted by corneal transplantation. Cytomegalovirus, which can be isolated from tears,² is a lymphotrophic organism. Because lymphocytes are present in the central and midperipheral cornea,^{3,4} there is the possibility that cytomegalovirus could be transmitted by a corneal transplant.

The method of detecting seroconversion of cytomegalovirus in our study was a fourfold rise in anticytomegalovirus IgG titer. The first two references cited by Dr. Pepose to support his contention that there is a lack of correlation between cytomegalovirus serology and clinical cytomegalovirus retinitis concern immunosuppressed patients who are not comparable to the normal immunocompetent population we studied. We agree that the serologic response to cytomegalovirus may fluctuate throughout life, but not to the extent of a fourfold rise in titer. A change in IgG status was deemed more useful than IgM status because IgM antibody levels rise and fall within a short period after infection, providing a smaller window for detection, and not all patients exposed to cytomegalovirus will show a significant rise in IgM titer.

We did not perform more sophisticated studies to detect seroconversion because their considerable expense and relative inaccessibility would be of limited value in a clinical setting. If the serologic screening test fails to demonstrate a pattern of seroconversion in the corneal recipients, further testing would not be warranted.

Finally, we did not assert that information from this study would throw light on the transmission of hepatitis virus. We did make reference to human immunodeficiency virus and stated that because cytomegalovirus and human immunodeficiency virus were both lymphotrophic viruses, "information about cytomegalovirus transmission might be useful in investigating whether AIDS would be transmitted by corneal transplantation."

We continue to believe that useful epidemiologic and clinical information may be gained by studying the possible transmission of cytomegalovirus by penetrating keratoplasty.

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Minneapolis, Minnesota
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Ocular Involvement in Mycotic Sinusitis Caused by Bipolaris

EDITOR:

In the article "Ocular involvement in mycotic sinusitis caused by *Bipolaris*," by W. M. Jay, R. W. Bradsher, B. LeMay, N. Snyderman, and E. J. Angtuaco (Am. J. Ophthalmol.

105:366, April 1988), the authors describe a healthy 17-year-old and an 18-year-old, both of whom suffered from a fungus infection of the sinuses. Is it not possible that these patients could have developed the infection from contaminants that might be found in street cocaine?

In this day and age this possibility does not seem far-fetched.

FRANK J. BEASLEY, M.D. Fort Lauderdale, Florida

Reply .

EDITOR

Dr. Beasley's question is both timely and relevant, given the widespread illicit use of drugs.

Reviewing the literature, we discovered only two cases of sinusitis as a complication of cocaine abuse. In the first, Schweitzer¹ described a 29-year-old woman with a five-year history of "allergic-like" symptoms including chronic facial fullness, postnasal drainage, halitosis, intermittent epistaxis, and rhinitis. The patient admitted to frequent "binging" by snorting 1 to 3.5 g of cocaine daily. Results of head and neck examinations disclosed complete bony and cartilaginous necrosis of the nasal septum, erosion of the medial walls of the maxillary sinuses, friability of the mucosal lining of the nasal and sinus cavities, saddlenose deformity, and objective rhinolabia. A computed tomographic scan demonstrated bony destruction of the medial and superolateral walls of the ethmoid and maxillary sinus with sinus opacification.

In the second case, Newman and associates² described a 43-year-old man with bilateral decreased visual acuity and asymmetric optic nerve head swelling. The patient admitted to 15 years of daily intranasal cocaine use. Magnetic resonance imaging showed extensive bony destruction of the nasal cavity, paranasal sinus, floor of the anterior cranial fossa, and anterior surface of the clivus.

One of us (N.S.), an otolaryngologist, questioned both of our patients regarding cocaine use. Both patients appeared to be reliable, and both denied illicit drug abuse. Additionally, intranasal examination did not support chronic cocaine use.

WALTER M. JAY, M.D.
ROBERT W. BRADSHER, M.D.
BRAD LEMAY, M.D.
NANCY SNYDERMAN, M.D.
EDGARDO J. ANGTUACO, M.D.
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BOOK REVIEWS

Edited by H. Stanley Thompson, M.D.

Management of Ocular, Orbital and Adnexal Trauma. Edited by Thomas C. Spoor and Frank A. Nesi. New York, Raven Press, 1987, 459 pages, index, illustrated. \$88.50

Reviewed by LEONARD PARVER Washington, D.C.

This 459-page text is designed to bridge the gap between the various medical disciplines that interact in the management of ocular, orbital, and adnexal trauma.

The first portion deals with ocular trauma and consists of 13 chapters, which provide a general overview of a number of important topics in the management of patients with severe ocular trauma. A notable deficiency, however, is the lack of a chapter dealing with injury prevention. The second section consists of seven chapters dealing with orbital trauma. I found this section to be the most informative. It is the basis for understanding the importance of a team approach to the orbital injury patient. The final section deals with eyelid trauma and consists of three chapters.

This is an ambitious endeavor, dealing with an area where a number of subspecialty groups interact. As in any text with multiple authors, there is some variability in the quality of the chapters. In general, the book gives an overview of what can be a complicated subject and would be particularly useful to those physicians who are frequently involved in the care of patients with eye injuries.

Clinical Light Damage to the Eye. Edited by David Miller. New York, Springer-Verlag New York, Inc., 225 pages, index, illustrated. \$89

Reviewed by Jose S. Pulido Iowa City, Iowa

The stated purpose of this book is to make accessible to clinicians the recent explosion of work on ocular phototoxicity. It will be valuable to ophthalmologists because it helps to put phototoxicity in perspective.

The first chapter, in which the units of energy are discussed, is an attempt to simplify a complex subject, but it is sometimes difficult to follow. In general, however, the book is worthwhile and enjoyable reading. The chapters on glaucoma and cornea and their relation to phototoxicity offer some thought-provoking speculation.

Only one paragraph in the book is devoted to retinal damage caused by operating microscopes. Considering recent emphasis on this problem, more elaboration might have been helpful for the clinician. This text can be easily read and will be valuable to those who are not actively engaged in research in this field. The book provides a nice overview of an important subject and should be read by all residents, fellows, and practicing clinicians in ophthalmology.

Macroscopic Ocular Pathology. By F. H. Stefani and G. Hasenfratz. New York, Springer-Verlag New York, Inc., 1987. 178 pages, index, illustrated. \$139

Reviewed by Don H. NICHOLSON and SANDRA FRAZIER-BYRNE Miami, Florida

The authors' stated primary goal is to provide an atlas of color photographs of the macroscopic appearance of dissected eyes to "be used with textbooks on anatomy and ocular pathology." The objective is "not to cover every known pathologic condition, but to include illustrations which may contribute to the understanding of clinical findings." Second, the authors present "accompanying typical echograms" to complement some of the macroscopic color pictures.

The 250 color plates are magnificent, museum-quality photographs of specimens processed in the authors' general pathology laboratory; they would be even more valuable if accompanied by a scale rule.

Illustration of gross ocular pathology alone has inescapable limitations. Clinical histories are absent or inadequate for most of the cases.

There is undue emphasis on endstage conditions. Some of the gross photographs are subject to conflicting interpretations, which could be resolved by addition of photomicrographs. The vitreous in Figure 5.16 appears clearly detached, but the authors interpret it otherwise. Figure 10.20, the gross photograph of an "amelanotic juxtapapillary tumor with massive optic nerve extension," is said to represent an amelanotic melanoma occurring after mastectomy for breast cancer. This unusual combination of history and gross pathology should be substantiated by a photomicrograph, to assure the critical reader that it is not a juxtapapillary metastasis. Figure 4.16 appears to be a good example of congenital hypertrophy of the retinal pigment epithelium, although the authors contend "from the macroscopic appearance, it may be speculated that toxoplasmosis was the cause of the scar." A photomicrograph would settle the issue.

The text that accompanies the macrographs presents clinical advice that is at times questionable, at times wrong. For example, the authors indicate that background diabetic retinopathy and macular edema should be treated with panretinal photocoagulation. They also advocate "intraocular microsurgical vitrectomy" for treatment of rubeosis iridis (page 48).

Finally, this is not a text of macroscopicechographic correlations. The ultrasound illustrations are not taken from the eyes studied pathologically, but are, rather, "typical echograms" selected to illustrate the conditions under consideration. The authors and the reader thus lose the opportunity to make critical echographic-pathologic comparisons and to examine carefully assumptions made in standardized A scan echography. The final frustration to the student in search of pathologicechographic correlation comes from cases in which the eye was erroneously enucleated because of a misleading ultrasound test, but the ultrasound selected to illustrate the condition is from a different case (Figures 5.5, 10.3, and 10.4).

Books Received

Differential Diagnosis of Eye Diseases, ed. 2. By Hans Pau. Translated by F. C. Blodi and C. F. Blodi. New York, Thieme Medical Publishers, Inc., 1988. 479 pages, index, illustrated. \$125

This is a revised and enlarged edition, translated by the Drs. Blodi, father and son. Since the author has tried to cover all of clinical ophthalmology in a single volume, some minor fault can be found on almost every page. But each page is also likely to provide a new insight or an uncommon reference, derived from the European point of view. One has to admire the book's organization, economy of style, and especially the rich supply of clear photographs that appear at an average rate of one per page, half of which are in color.

Tissue Banking. Edited by Alice R. Barr and Kenneth Fawcett. Arlington, Virginia, American Association of Blood Banks, 1987. 157 pages, index, illustrated. \$25

Contains a chapter on the role of the Eye Bank in ophthalmology.

Medical Abbreviations: 5500 Conveniences at the Expense of Communications and Safety, ed. 4. By Neil M. Davis. Huntingdon Valley, Penn., Neil M. Davis Associates, 1988. Softcover, 140 pages, \$7.95 (\$5.65 if order is 20 or more).

This edition contains 5,500 abbreviations, acronyms, and symbols (a 70% increase over the first edition published in 1983) together with 7,480 possible meanings. Its value as a reference increases by seventyfold.

Immunopathologie de l'oeil. By J.-P. Faure, E. Bloch-Michel, P. le Hoang, and E. Vadot. Paris, Masson, 1988. 430 pages, index, illustrated.

A detailed textbook in French on the immunopathology of the eye prepared for the French Ophthalmology Society.

ABSTRACT DEPARTMENT

Edited by David Shoch, M.D.

Acta Ophthalmologica

Light microscopical and scanning electron microscopical examinations of deposits on disposable constant wear lenses. Prause, J. U., Brincker, P., Dryer, V., and Vangsted, P. (Eye Pathol. Inst., Frederik V's Vej 11,5, Dk-2100 Copenhagen O, Denmark). Acta Ophthalmol. 66:3, 1988.

Twenty-two patients, aged 18 to 48 years with healthy eyes, were fitted with disposable contact lenses molded from hydroxethyl methacrylate and hydroxyethyl acrylate in order to evaluate the wearability of the lenses. The lenses were worn for different lengths of time, with a median of seven days and a range of one to 43 days. All patients wore the lenses successfully without any harm to their corneas. The lenses were examined with light microscopy and although there were some deposits that were periodic acid-Schiff positive, no calcium or lipid deposits were found and no bacteria or fungi were demonstrable. This type of lowcost, disposable soft contact lens allowing for frequent replacement should prevent some of the more severe complications associated with extended-wear lenses. (6 figures, 1 table, 31 references)—David Shoch

British Journal of Ophthalmology

Familial uveal melanoma. Canning, C. R., and Hungerford, J. (Moorfields Eye Hosp., City Rd., London EC1V 2PD, England). Br. J. Ophthalmol. 72:241, 1988.

The authors described two families in which two members each had uveal melanomas. In one family, a sister and brother and in the second family, a mother and son were affected. Uveal melanomas are uncommon and it is difficult to estimate the probability that two members of the same family would develop melanonas by chance alone. However, a report of a

family in which five members were affected in three generations indicates that some factor other than chance is involved. As yet, there have been no genetic markers identified for melanoma of the choroid. (1 table, 27 references)—David Shoch

Two cases of primary bilateral malignant melanoma of the choroid. Seregard, S., Daunius, C., Kock, E., and Popovic, V. (Dept. Ophthalmol., Karolinska sjukhuset, Box 60500, 10401 Stockholm, Sweden). Br. J. Ophthalmol. 72:244, 1988.

The authors examined two patients with bilateral malignant melanomas of the choroid. In the first patient, both eyes were enucleated and histologic confirmation was obtained. In the second patient, only one eye was enucleated and the other was irradiated. Both patients are alive and well some five years after the enucleations. (9 references)—David Shoch

Comparative evaluation of oculokinetic perimetry and conventional perimetry in glaucoma. Alvarez, E., Damato, B. E., Jay, J. L., and McClure, E. (Tennant Inst. Ophthalmol., Western Infirm., Glasgow G11 6NT, Scotland). Br. J. Ophthalmol. 72:258, 1988.

The authors described a new technique to assess the visual field, which they call oculo-kinetic perimetry. In this technique there is a central fixation target and a series of numbered targets along each meridian, ranging from one to 100. The patients are asked to fix on the numbers in sequence and to report whether the central fixation target disappears. The scotomas can be plotted by inversion of the test results. The authors used this technique in 64 eyes of 37 patients who had unequivocal visual field loss by other tests. The results were identical in 56 (88%) of the eyes tested and comparable in another four (6%). The test is simple, can

be carried out by untrained persons, and might be a useful screening device for glaucoma. (2 figures, 4 tables, 3 references)—David Shoch

Therapeutic limitations of argon laser trabeculoplasty. Fink, A. I., Jordan, A. J., Laq, P. N., and Fong, D. A. (110 Remsen St., Brooklyn NY 11201). Br. J. Ophthalmol. 72:263, 1988.

This study was designed to follow the course of intraocular pressure control in 61 patients (82 eyes) who were treated with argon laser trabeculoplasty. At a mean follow-up time of about two years, the success rate was the same as it had been at the end of three months, roughly 75%. However, at the end of 42 months, the success rate had declined to 45%. There appeared to be no difference between right and left eyes, nor any difference between eyes that received 100 burns at 1 W or 65 burns at 850 mW. Eight eyes showed continued visual field loss despite reduction of intraocular pressure below the baseline level. Although the success rate decreased over time, trabeculoplasty deferred the visual loss associated with glaucoma and had a lower risk than filtering surgery. It also had fewer side effects than carbonic anhydrase inhibitor therapy. (6 figures, 2 tables, 35 references)—David Shoch

British Journal of Radiology

Ocular lens dose in cerebral vascular imaging. Casselden, P. A. (X-ray Dept., Special Invest. Suite, Royal Free Hosp., Pond St., London NW3 2QG, England). Br. J. Radiol. 61:202, 1988.

The authors placed thermoluminescence dosimeters on the foreheads of ten patients undergoing angiography for subarachnoid hemorrhages. In comparing conventional angiography with digital subtraction angiography, there was a significant difference in the dose exposure at the level of the ocular lens. The actual dose received in digital subtraction angiography was 0.327 rad. Conventional angiography delivered a dose of 60 rad. The use of an undercouch tube in digital subtraction angiography and an increased focus-lens distance

are the major factors contributing to the differences in lens dose. To reduce danger to the lens, digital subtraction angiography should be the method of choice for study of cerebral blood vessels. (2 tables, 2 references)—David Shoch

Diabetologica

Diabetic eye disease in Central Africa. Rolfe, M. (Wick Manor, Curry Rivel, Langport, Somerset TA10 ONW, England). Diabetologia 31:88, 1988.

Of 600 diabetic patients from nine hospitals in the Copperbelt region of Zambia, 204 (34%) had retinopathy and 78 (13%) had cataracts. In this entire group only one patient was blind from proliferative retinopathy, whereas 24 (4%) of the patients were blinded by cataracts. Thus, in the areas of the world where ophthalmic care is less available, cataracts probably represent a more common cause of blindness in diabetic patients than proliferative diabetic retinopathy. (9 tables, 27 references)—David Shoch

Journal of the Royal Society of Medicine

The eye and inherited metabolic disease: a review. Michalski, A., Leonard, J. V., and Taylor, D. S. I. (Inst. Child Health, 30 Guilford St., London WC1, England). J. R. Soc. Med. 81:286, 1988.

The authors present a table of abnormalities associated with a variety of metabolic diseases. The list of the ocular structures starts with the conjunctiva and sclera and continues through the optic nerve and disorders of ocular movement and position. Some of the more classic metabolic diseases with ocular findings are also reviewed in detail. These include tyrosinemia type II, gyrate atrophy with hyperornithinemia, abetalipoproteinemia, Zellweger's syndrome and related disorders, and homocystinuria. (4 figures, 1 table, 6 references)—David Shoch

Nature

Retinal astrocytes are immigrants from the optic nerve. Watanabe, T., and Raff, M. C. (Dept. Biol., Medawar Bldg., Univ. College London, London WC1E 6BT, England). Nature 332:834, 1988.

To determine the source of retinal astrocytes, the authors stained whole mounts of the retinas of perinatal rats with antibodies against glial fibrillary acidic protein. They found that glial fibrillary acidic protein-positive cells were first seen between embyronic days 18 and 19 and were largely confined to the optic nerve head. Three days later, the cells were also present in the retina but only within approximately 800 µm from the edge of the nerve head. By postnatal day 9, they had reached the periphery of the retina. These findings are consistent with the view that astrocytes migrate from the optic nerve head to the rest of the retina and do not necessarily migrate with blood vessels. (2 figures, 2 tables, 38 references)—David Shoch

New England Journal of Medicine

Macular hemorrhage in the aging eye: the effects of anticoagulants. Kingham, J. D., Chen, M. C., and Levy, M. H. (Sarasota Retina Inst., Sarasota, FL 34239). N. Engl. J. Med. 318:1126, 1988.

Of 109 elderly patients with macular hemorrhage, all of whom were taking anticoagulants or antiplatelet drugs, 40% were using aspirin and the rest were taking dipyridamole, ibuprofen, dicumarol, or another antiplatelet drug. Elderly patients with macular degeneration who take any of these drugs, particularly aspirin, should be carefully monitored. (1 table, 4 references)—David Shoch

Medjugorge maculopathy. Campo, R. V., Sipperley, J. O., Hall, G., and Rappazzo, J. A. (Dept. Ophthalmol., St. Luke's Hosp., Phoenix, AZ 85006). N. Engl. J. Med. 318:1207, 1988.

Two pilgrims to a small farming village in Yugoslavia called Medjugorge, where people

by the thousands visit to stare into the sun in the hope of seeing apparitions of the Virgin Mary, returned with loss of vision. In the first patient, the loss involved only one eye and the visual acuity gradually improved from 20/70 to 20/30. The second patient had bilateral involvement; visual acuity gradually improved from 20/200 to 20/50. Both patients still have central scotomas. In the presence of unexplained visual loss and central scotomas, it would be appropriate to inquire about a history of such pilgrimages. (6 references)—David Shoch

Transplantation

HLA antigens in ocular tissues. Abi-Hanna, D., Wakefield, D., and Watkins, S. (School of Pathol., Univ. New South Wales, Kensington, N.S.W., 2033, Australia). Transplantation 45:610, 1988.

Using indirect immunofluorescence and immunoperoxidase staining, the authors examined various ocular tissues for class I and class II human leukocyte antigens in 24 human eyes obtained at autopsy within 24 hours of death. Most of the cells in the eye did not express class I or class II human leukocyte antigens, with the exception of blood vessel endothelium, which is uniformly class I positive. This was also true for the conjunctival epithelial cells. The corneas were not studied in this group of eyes because they were used for transplantation. This lack of expression of human leukocyte antigens may be responsible for the relative immunologic privilege in the eye. (5 figures, 23 references) —David Shoch

Successful engraftment of high-risk corneal allografts with short-term immunosuppression with cyclosporine. Miller, K., Huber, C., Niederwieser, D., and Gottinger, W. (Dept. Ophthalmol., Univ. Innsbruck, Anichstr. 35, 6020 Innsbruck, Austria). Transplantation 45:651, 1988.

Fifteen patients who had vascularization in all four quadrants of the cornea were treated with systemic cyclosporine beginning one hour after corneal transplantation. The initial dose was given by intravenous infusion; after 24 hours, the patients were given cyclosporine, 5

mg/kg of body weight/day. This therapy was continued for 12 weeks. In addition to the systemic cyclosporine, the patients also received 0.1% dexamethasone eyedrops five times daily. Twelve of 15 patients maintained clear grafts for eight to 36 months. Two patients had graft rejection episodes, and in the third patient, cyclosporine treatment was discontinued because of occlusion of a temporal artery. This patient had an acute rejection on the

seventh day after discontinuing systemic cyclosporine. There were graft rejection episodes after cessation of systemic immunosuppression but these were treated successfully with corticosteroids. The only side effects noted in the three-month treatment with cyclosporine were transient hypertension in three patients and aggravation of preexisting hypertension in one patient. (1 table, 7 references)—David Shoch

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NEWS ITEMS

Send News Items to American Journal of Ophthalmology 435 N. Michigan Ave., Suite 1415 Chicago, IL 60611

The Journal invites readers to submit announcements concerning meetings, postgraduate courses, lectures, honors, and appointments. Each item must be typed double-spaced on bond paper with 1½-inch margins. Only one news item should be submitted on each page. Announcements concerning meetings and courses must contain the title, location, dates, sponsors, and address required for additional information. Each item must not exceed 75 words in length. Announcements of meetings and courses must be received at least four months before the event.

Seventh European Intraocular Lens Implant Council Meeting

The Seventh European Intraocular Implant Lens Council meeting will be held Aug. 27–31, 1989, in Zurich, Switzerland. For further information, write A K M Congress Service, 57 Clarastrasse, CH-4005, Basel, Switzerland.

Third Annual East African Ophthalmic Plastic and Reconstructive Surgery Symposium

The Third Annual East African Ophthalmic Plastic and Reconstructive Surgery Symposium will be held Jan. 25 to Feb. 8, 1990, in Tanzania. For further information, write Stephen L. Bosniak, M.D., 300 Central Park West, New York, NY 10024.

Sally Letson Foundation and University of Ottawa: Neuro-Ophthalmology Symposium

The Sally Letson Foundation and the Department of Ophthalmology of the University of Ottawa will present a Neuro-Ophthalmology Symposium, Sept. 16 and 17, 1988, in Ottawa, Canada. For further information, write Mrs. Karen Reddie, 267 O'Connor St., Ottawa, Canada K2P 1V3.

Saint Luke's Hospital: Third Annual Tilles-Weidenthal Lecture

Mark S. Blumenkranz will give the Saint Luke's Hospital Third Annual Tilles-Weidenthal Lecture, Sept. 24, 1988, in Cleveland, Ohio. For further information, write Daniel T. Weidental, M.D., Division of Ophthalmology, Saint Luke's Hospital, 11311 Shaker Blvd., Cleveland, OH 44104.

University of California, Irvine: Ocular Drug Therapy Update-1988

The University of California, Irvine, will present Ocular Drug Therapy Update–1988, Oct. 7, 1988, in Irvine, California. For further information, write Gloria Cotto, Department of Ophthalmology, University of California, Irvine, School of Medicine, Irvine, CA 92717.

Puerto Rico Ophthalmological Society: Annual Ophthalmological Convention

The Puerto Rico Ophthalmological Society will hold its Annual Ophthalmological Convention, Nov. 10–13, 1988, in San Juan, Puerto Rico. For further information, write Victor M. Diaz Bonnet, M.D., Box 1184, Hato Rey, Puerto Rico, 00919.

American Association for the History of Medicine, Inc.: 62nd Annual Meeting

The American Association for the History of Medicine will hold its 62nd annual meeting, April 27–30, 1989, in Birmingham, Alabama. For further information, write Bill Weaver, Box 700, University of Alabama, Birmingham, AL 35294.

Eye Foundation of Kansas City: Phacoemulsification Course

The Eye Foundation of Kansas City will hold a Phacoemulsification Course, Sept. 10 and 11, 1988, in Kansas City, Missouri. For further information, write Cecelia Corteville, Eye Foundation of Kansas City, P.O. Box 24687, Kansas City, MO 64131.

Johns Hopkins Medical Institutions: Diabetic Retinopathy in 1988

The Wilmer Ophthalmological Institute of the Johns Hopkins Medical Institutions will sponsor a course, Diabetic Retinopathy in 1988, Sept. 23, 1988, in Baltimore, Maryland. For further information, write Program Coordinator, Office of Continuing Education, The Johns Hopkins Medical Institutions, Turner 22, 720 Rutland Ave., Baltimore, MD 21205.

University of Miami: Neuro-Ophthalmology Course

The University of Miami, Bascom Palmer Eye Institute will sponsor a Neuro-Ophthalmology

course, Dec. 8–10, 1988, in Key Biscayne, Florida. For further information, write Bascom Palmer Eye Institute, P.O. Box 015869, Miami, FL 33101.

Virginia Mason Clinic: First Cornea-Retina Conference

The Section of Ophthalmology of the Virginia Mason Clinic will hold its first Cornea-Retina Clinical Conference, Sept. 24, 1988, in Seattle, Washington. For further information, write Linda Orgel, Virginia Mason Clinic, 1100 9th Ave., Seattle, WA 98101.

North Carolina-South Carolina Society of Ophthalmology: Annual Meeting

The Annual Meeting of the North Carolina-South Carolina Society of Ophthalmology will be held Oct. 27–29, 1988, in Asheville, North Carolina. For further information, write Carol T. Russell, Executive Director, North Carolina Society of Ophthalmology, Inc., P.O. Box 27167, Raleigh, NC 27611.

University of North Carolina: Ophthalmology Residents' Day

The Department of Ophthalmology of the University of North Carolina will hold the Ophthalmology Residents' Day, Dec. 3, 1988, in Chapel Hill, North Carolina. For further information, write Baird S. Grimson, M.D., Department of Ophthalmology, CB#7040, 617 Clinical Sciences Building, University of North Carolina, Chapel Hill, NC 27599-7040.

Benign Essential Blepharospasm Research Foundation: Sixth International Conference

The Benign Essential Blepharospasm Research Foundation will hold its Sixth International Conference, Aug. 26, 1988, in Cambridge, Massachusetts. For further information, write Mrs. Robert O. G. Bruce, Benign Essential Blepharospasm Research Foundation, Inc., P.O. Box 12468, Beaumont, TX 77706.

St. Luke's Medical Center: Fifteenth Annual Frontiers in Ophthalmology

St. Joseph's Hospital & Medical Center, St. Luke's Medical Center, and Prentice Eye Institute will sponsor the Fifteenth Annual Frontiers in Ophthalmology, Feb. 9–11, 1989, in Scottsdale, Arizona. For further information, write Christine Campbell, Campbell Meeting

Management, 4659 S. Lakeshore Dr., Suite D., Tempe, AZ 85282.

University of Maryland: Current Concepts in Ophthalmology

The University of Maryland will sponsor a conference, Current Concepts in Ophthalmology, Sept. 23, 1988, in Baltimore, Maryland. For further information, write The Program of Continuing Education, University of Maryland School of Medicine, 10 S. Pine St., Suite 300, Baltimore, MD 21201.

Manhattan Eye, Ear and Throat Hospital: Ophthalmology Seminar

The First Annual Manhattan Eye, Ear and Throat Hospital Ophthalmology Seminar will be held Sept. 16 and 17, 1988, in New York, New York, for further informtion, write Martha Klapp, Department of Ophthalmology, Manhattan Eye, Ear and Throat Hospital, 210 E. 64th St., New York, NY 10021.

Fifth Annual Glaucoma Symposium

IOLAB Pharmaceuticals will sponsor the Fifth Annual Glaucoma Symposium, March 5–7, 1989, in Grand Cayman, British West Indies. For further information, write David Townsend, Associates in Medical Marketing Co., Inc., 9 Pheasant Run Rd., Newtown, PA 18940.

Alcon Research Institute Prizes

Each year an independent Advisory Committee nominates and selects individuals who have made important contributions to vision research. A monetary award is given with the expectation that the awardees will apply it to further their research. An annual awards symposium is held in celebration of the awardees. The first symposium was held in Fort Worth, Texas, in 1984, and the most recent one March 17 and 18, 1988. An award of \$50,000 was given to each of the following scientists in 1988: David Ben Ezra, Hadassah University, Jerusalem, Israel; Eliot Berson, Harvard Medical School, Boston, Massachusetts; Ian Grierson, Institute of Ophthalmology, London, England; Elizabeth Hay, Harvard Medical School, Boston, Massachusetts; Edward L. Howes, Jr., University of California, San Francisco, California; Tokindo Okada, National Institute of Basic Biology, Okazaki, Japan; Beryl J. Ortwerth, University of Missouri, Columbia, Missouri;

Robert A. Prendergast, Johns Hopkins University School of Medicine, Baltimore, Maryland; Charles E. Riva, Scheie Eye Institute, Philadelphia, Pennsylvania; Bernard Schwartz, Tufts New England Medical Center, Boston, Massachusetts; E. Michael van Buskirk, University of Oregon, Portland, Oregon; and J. Samuel Zigler, Jr., National Institutes of Health, Bethesda, Maryland.

International Society of Ocular Toxicology

The International Society of Ocular Toxicology was founded at the first International Congress of the Society in Toronto, Canada, June 4–8, 1988. The elected officers are: Otto Hockwin, president; Sidney Lerman, presidentelect; F. T. Fraunfelder, past-president; Keith Green, secretary-treasurer; and P. S. Kaplan, I. Weise, and K. Sasaki, councilors.

New Orleans Academy of Ophthalmology: New Officers

The officers of the New Orleans Academy of Ophthalmology for 1988–1990 are Miles H.

Friedlander, president; Rodney F. Kalil, president-elect; Rudolph M. Franklin, vice-president; Delmar R. Caldwell, secretary; and William F. Rachal, treasurer.

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Massimo G. Bucci

Massimo G. Bucci was appointed chief of the Second Clinica Oculistica Dell'Universita di Roma.

Anders Heijl

At the Eighth meeting of the International Perimetric Society, Anders Heijl, University of Lund, Sweden, was elected the new president of the Society. He succeeds Stephen Drance of Vancouver, British Columbia.

AMERICAN JOURNAL OF OPHTHALMOLOGY

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ORIGINAL ARTICLES

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Ultraviolet Transmittance of Intraocular Lenses

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Expulsive Choroidal Hemorrhage

Pseudophakic Bullous Keratopathy

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Endothelial Function in Fuchs' Dystrophy

Wilson, Bourne, O'Brien, Brubaker

Corneal Shields for Keratitis

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Lacquer Cracks in Pathologic Myopia

Klein, Green

Annular Macular Degeneration

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Optic Nerve Function and Liquid Silicone

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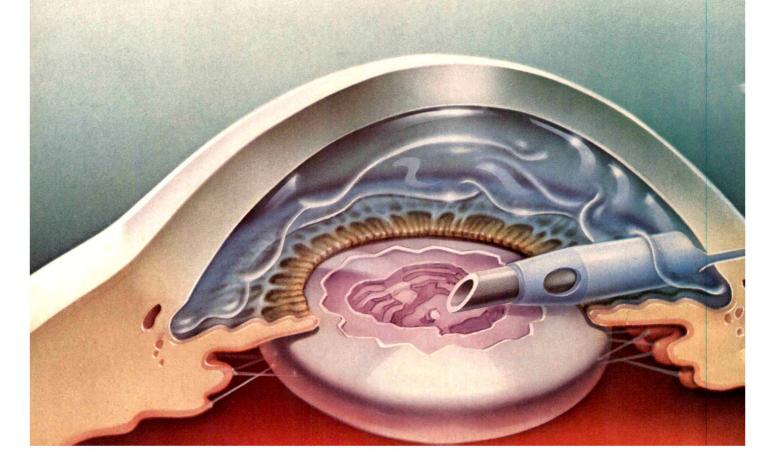
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Thymoxamine Reverses Phenylephrine-Induced Mydriasis

Susan J. Relf, B.S., N. Ziai Gharagozloo, M.D., Gregory L. Skuta, M.D., Wallace L. M. Alward, M.D., Douglas R. Anderson, M.D., and Richard F. Brubaker, M.D.

We performed a randomized double-masked evaluation of the alpha-adrenergic blocking agent thymoxamine (0.1%) as compared to placebo for the reversal of phenylephrineinduced mydriasis. Topically applied thymoxamine reversed the mydriasis from a single drop of 2.5% phenylephrine in 36 of 40 eyes (90%) within one hour. The mydriasis was completely reversed in 25 of 40 eyes (63%). Eyes with blue irides responded more quickly and more completely than did those with brown irides. The 40 contralateral eyes, which had also been dilated with phenylephrine, remained dilated or dilated further after receiving a placebo eyedrop. Twenty subjects (50%) reported mild transient ocular irritation upon instillation of thymoxamine. Thymoxamine was useful in individuals with narrow anterior chamber angles who were at risk of acute closed-angle glaucoma following dilation with an adrenergic agent.

Accepted for publication June 8, 1988.

From the Department of Ophthalmology, Mayo Clinic and Foundation, Rochester, Minnesota (Ms. Relf and Drs. Gharagozloo and Brubaker) and the Bascom Palmer Eye Institute, Department of Ophthalmology, University of Miami School of Medicine, Miami, Florida (Drs. Skuta, Alward, and Anderson).

This study was supported in part by National Institutes of Health research grant ROI EY 00634 (Dr. Brubaker); National Research Service Award T32 EY 07021 (Dr. Skuta); Research to Prevent Blindness, Inc.; IOLAB Pharmaceuticals, Claremont, California; National Glaucoma Research, a program of the American Health Assistance Foundation, Rockville, Maryland; and the Mayo Foundation, Rochester, Minnesota. This study was presented at the annual meeting of the Association for Research in Vision and Ophthalmology, Sarasota, Florida, May 2, 1988.

Reprint requests to Richard F. Brubaker, M.D., Department of Ophthalmology, Mayo Clinic, Rochester, MN 55905.

THYMOXAMINE is an alpha-adrenergic blocking agent that competes with norepinephrine and other adrenergic agonists at the postjunctional alpha-1-adrenoreceptor. 1 It has been used in the reversal of phenylephrineinduced mydriasis,² and consistently produces miosis without affecting the intraocular pressure, the rate of aqueous humor formation, or the facility of outflow of aqueous humor. 3,4 It does not cause shallowing of the anterior chamber or ciliary spasm. 5,6 Thymoxamine has no beta-blocking effect and little or no antihistamine effect.7 It has also been used in the treatment of acute closed-angle glaucoma,8 and in the diagnosis of closed-angle glaucoma.9 Thus, without causing undesirable side effects, thymoxamine safely and rapidly reverses the effects of an adrenergic mydriatic drug, reducing the risk of acute closed-angle glaucoma and facilitating the return to normal, comfortable vision and appearance.

The most frequently reported dose of thymoxamine, formulated in sterile saline, 0.5%, is considerably higher than the minimum effective concentration of 0.01%.1 A recent doseresponse study showed 0.1% thymoxamine to be clinically efficacious in reversing phenylephrine-induced mydriasis, with acceptable rapidity of response and minimal side effects. 10 The purpose of this study was to determine the efficacy and time course of the reversal of phenylephrine-induced mydriasis by a 0.1% thymoxamine solution recently formulated for

topical ophthalmic use.

Material and Methods

We performed a double-masked evaluation of the active drug (0.1% thymoxamine hydrochloride) vs a placebo (vehicle of 1.0% polyvinyl alcohol, polyethylene glycol, dextrose, edetate sodium, and 0.01% benzalkonium chloride). Thymoxamine was randomly assigned to one eye, and the placebo to the other eye of the same subject. The study was conducted at the Bascom Palmer Eye Institute and the Mayo Clinic.

The study included 20 subjects at each site, 12 women and 28 men. The mean age of the participants was 29 ± 7 years (mean \pm S.D.). Subjects with light (blue) and dark (brown) irides were obtained in equal numbers. Pregnant or nursing women were excluded from the study. Volunteers were not allowed to wear contact lenses during the course of the study. All subjects had normal, healthy eyes, as determined by ophthalmic evaluation including history, test of visual acuity, slit-lamp examination, Goldmann applanation tonometry, and direct ophthalmoscopy. Written informed consent was obtained at the time of the initial screening examination.

Pupil measurements were made to the nearest 0.5 mm, using the reticule in the observer telescope of a Goldmann perimeter under standard lighting conditions of 3.2 millilamberts in the bowl.

The study began with the measurement of baseline pupil diameters, followed by the instillation of two drops of 2.5% phenylephrine, five minutes apart, into both eyes of each subject. Forty minutes after the second drop of phenylephrine was instilled (time 0), the pupil diameters were again measured. One eye then received one drop of the active drug and the fellow eye, one drop of placebo, according to a randomized code. Neither the subject nor the investigator were aware of which eye received the active drug and which the placebo. Pupil diameters were again measured at intervals of ten, 20, 30, and 60 minutes after instillation of the test drops.

Subjects were asked to comment on any symptoms or adverse reactions experienced throughout the course of the study. They were also instructed to report to the investigator any symptoms or adverse reactions that occurred after the completion of the study, and which might reasonably be suspected of being study-related.

Follow-up ophthalmic examinations were performed in the same manner as the initial screening examinations within one week after each subject's completion of the study.

Data were evaluated using analysis of variance and Student's t-tests. P < .05 was considered significant.

Results

After phenylephrine was instilled, the pupil dilated from an average baseline diameter of 4.6 ± 1.0 mm (mean \pm S.D.) to an average diameter at time 0 of 6.4 ± 1.1 mm in eyes destined to receive thymoxamine. In eyes destined to receive placebo, the pupil dilated from an average baseline diameter of 4.5 ± 1.0 mm to an average diameter of 6.4 ± 1.1 mm. Analysis of variance did not show any influence of study site (Mayo Clinic vs Bascom Palmer Eye Institute) or iris color (light vs dark) on the dilated pupil diameter at time 0. The pupil size at this time was not uniform, ranging from 4 to 9 mm. Therefore, the subsequent response to thymoxamine or placebo was judged as a change in pupil diameter from its size at the time of thymoxamine or placebo instillation (time 0).

Following instillation of placebo, 30 of 40 eyes showed additional dilation for a short time, which increased the average pupil size for the group by 0.4 mm in the first 20 minutes. Thereafter, the average pupil size remained constant (Fig. 1). Two pupils constricted slightly (0.5 and 1.0 mm) one hour after receiving the placebo drop, but still measured well above their prephenylephrine baseline diameters. All other pupils remained dilated for the duration of observation.

Conversely, thymoxamine began to affect the pupil rapidly. Of the 40 eyes receiving thymoxamine, only 12 continued to dilate further in the first ten minutes. The average pupil diameter did not increase at ten minutes, and returned to its original baseline diameter within 30 to 60 minutes. The difference between placebo-treated and thymoxamine-treated eyes was statistically significant at ten minutes, and at each test time thereafter (Table 1). All but four pupils in the thymoxamine group became smaller after thymoxamine instillation, and 25 of 40 pupils (63%) returned to or became smaller than the prephenylephrine baseline. Seventeen pupils constricted to less than the prephenylephrine baseline; none of measured less than 3.0 mm in diameter.

Light and dark irides behaved differently in their response to both phenylephrine and thymoxamine (Figs. 2 and 3). Pupils of eyes with dark irides started smaller and responded less to phenylephrine than did those with light irides. Differences of 0.1 mm at the beginning of the study, and 0.4 mm at time 0, however, were not statistically significant. The response to thymoxamine was significantly slower and of

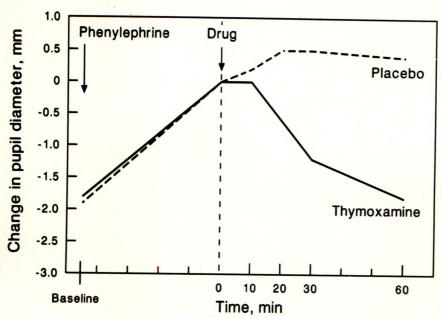


Fig. 1 (Relf and associates). Effects of thymoxamine and placebo on pupil diameter following dilation with phenylephrine.

lesser magnitude in eyes with dark irides (P < .001) from 20 through 60 minutes (Table 2). Only nine of the 20 eyes (45%) with dark irides had returned to baseline diameter or less at 60 minutes, whereas 16 of the 20 eyes (80%) with light irides had done so. All four eyes that failed to respond to thymoxamine had dark irides; of 17 eyes constricting to less than baseline, 14 had light irides.

Analysis of variance showed a difference in response to thymoxamine between eyes of light and dark irides as described above, but showed no such difference between the two study sites.

No serious complications were encountered during the course of the study. Side effects of mild burning or stinging, lasting less than two minutes, were reported by 16 of 40 subjects

TABLE 1
CHANGE IN PUPIL DIAMETER OVER TIME (MM)

	TIME (MIN)					
	10	20	30	60		
Thymoxamine		Ten e				
Mean	0.0	-0.6	-1.2	-1.8		
S.D.	0.5	1.0	1.3	1.1		
S.E.	0.1	0.2	0.2	0.2		
Placebo						
Mean	0.2	0.5	0.5	0.4		
S.D.	0.4	0.5	0.6	0.6		
S.E.	0.1	0.1	0.1	0.1		
Difference*	-0.2	-1.0	-1.7	-2.2		
P value	.013	<.001	<.001	<.001		

^{*}Paired one-tailed *t*-test; significant at P < .05.

(40%) upon receiving thymoxamine. Two subjects complained of similar symptoms bilaterally upon instillation of the test drops. Three subjects complained of burning and itching lasting less than 15 minutes and one subject reported a foreign-body sensation lasting for four hours, all in thymoxamine-treated eyes. Results of follow-up ophthalmic examinations were normal in all subjects.

Discussion

The experimental dose of 0.1% thymoxamine was efficacious in reversing phenylephrine-induced mydriasis. The miosis achieved in this study may be less than that previously reported after treatment with 0.5% thymoxamine, ^{1,2,4} but the other studies are not directly comparable to ours because the conditions of dilation were different.

The pupils of thymoxamine-treated eyes with light irides constricted rapidly and to a greater degree than did those with dark irides. Only four subjects, all dark-eyed, failed to respond to thymoxamine. Ocular pigment may delay or inhibit the delivery of thymoxamine to the receptor sites within the dilator muscle of the iris. Similar differences between irides of different colors were not reported in previous studies of 0.5% thymoxamine and pupil diameter without phenylephrine pretreatment.^{1,4}

Ocular pigmentation modifies the pharmacokinetics of both miotic and mydriatic drugs, binding them to the anterior uvea as discussed

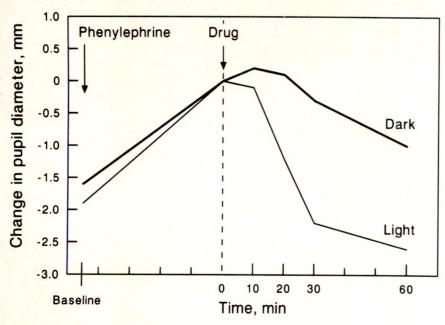


Fig. 2 (Relf and associates). Effects of thymoxamine on pupil diameter in eyes with light and dark irides following dilation with phenylephrine.

by Mishima. 11 At low drug concentrations in particular, this binding reduces the biophase concentration of the drug and its subsequent effects. When an excess of drug is administered, pigmentary binding creates a drug depot; subsequent drug release causes a reduced elimination rate constant, longer half-life, and longer duration of the drug's effect. A difference in pupillary constriction between eyes with light and dark irides has not been reported after instillation of 0.5% thymoxamine, but it was observed in this study using 0.1% thymoxamine, which suggests that the smaller dose may be low enough to allow

pigmentary binding to reduce thymoxamine's bioavailability relative to that of phenylephrine. Additionally, pigmentary binding of phenylephrine and the resulting drug depot within the dark iris might prolong phenylephrine activity in heavily pigmented eyes. Both mechanisms may be involved in thymoxamine's reduced efficacy in constricting the pupils of darkly pigmented eyes after dilation with phenylephrine.

A number of eyes, especially those with light irides, were found in this study to constrict to less than initial baseline values. The smallest of these had a pupil diameter of 3.0 mm at 60

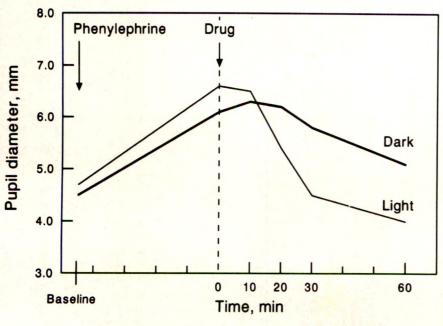


Fig. 3 (Relf and associates). Effects of thymoxamine on pupil diameter in eyes with light and dark irides following dilation with phenylephrine; absolute values.

TABLE 2
CHANGE IN PUPIL DIAMETER (MM) OVER TIME IN
THYMOXAMINE-TREATED EYES, LIGHT VS DARK
IRIDES

	TIME (MIN)					
	10	20	30	60		
Light irides						
Mean	-0.1	-1.2	-2.2	-2.6		
S.D.	0.7	0.9	0.9	0.8		
S.E.	0.2	0.2	0.2	0.2		
Dark irides						
Mean	0.2	0.1	-0.3	-1.0		
S.D.	0.4	0.5	0.7	0.9		
S.E.	0.1	0.1	0.2	0.2		
Difference	-0.3	-1.4*	-1.9*	-1.6*		
P value	.144	<.001	<.001	<.001		

^{*}Student's two-tailed *t*-test; significant at P < .05.

minutes after drug instillation, a size that might result in some inconvenience on the part of the patient under certain conditions, although none of the subjects in this study reported any such side effects. Given that the drug's half-life is reported to be ten hours, its effects might persist for some time. Although a lower dose might therefore be desirable in blueeyed individuals, some light-colored eyes and many dark-colored eyes had an incomplete response. Such eyes might require a higher dose or a second instillation to get the full desired effect. The minimal dose that is fully effective in an individual presumably depends not only on iris color and other biologic variability, but also on the agent and dose used for pupil dilation.

Minor side effects, largely sensations of mild burning and stinging, were associated with the administration of thymoxamine in 50% of the subjects (20 of 40). The only side effect of any duration was that of foreign-body sensation as reported by one subject, which resolved with no residual effect. Side effects thus appeared to be mild and of no lasting consequence.

We found 0.1% thymoxamine to be effective and safe in reversing the mydriasis of 2.5% phenylephrine, and thus of potential use in treating patients at risk of acute closed-angle glaucoma after dilation with an adrenergic agent. Eyes with light irides were more responsive to the drug than were those with dark irides. Patients receiving thymoxamine after

ophthalmic examination, especially those with light irides, might be left with miosis until the drug wears off. Patients with darkly pigmented irides may require a higher dose of thymoxamine or a second instillation of the drug to obtain the full effect.

ACKNOWLEDGMENT

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Variables Associated With Ultraviolet Transmittance Measurements of Intraocular Lenses

Sharon A. Miller, M.S., and Robert H. James, M.S.

We measured the spectral transmittance of 12 intraocular lenses with a spectroradiometer system that uses an integrating sphere input. We evaluated both low- and high-power lenses and varied the input aperture size between 1, 3, and 5 mm. These variations caused a significant difference in the transmittance characteristics of the intraocular lenses. Most significantly, the transmittance of the low-power model was two to six times greater than that of the high-power model in the cutoff region. The larger aperture resulted in, at most, a factor of two difference in transmittance. This effect was observed in intraocular lenses labeled both ultraviolet-absorbing and nonultravioletabsorbing.

THE ADULT CRYSTALLINE lens has a built-in protective mechanism against ultraviolet and infrared irradiation of the retina and absorbs most of the radiation at wavelengths below about 400 nm. 1 Because of these natural properties, the absorption of ultraviolet radiation in intraocular lenses has received much attention throughout industry and the medical community. In order to obtain accurate transmittance measurements of intraocular lenses, we used techniques of spectroradiometry with integrating sphere input optics instead of the more common method that uses spectrophotometry. We explored the effects of varying the aperture size and lens power on optical radiation transmittance, and compared the transmittance properties of intraocular lenses labeled both ultraviolet-absorbing and nonultravioletabsorbing. The purpose of this study is to examine an alternate technique for obtaining accurate ultraviolet transmittance data for intraocular lenses and to relate quantitatively the dependence of such data on refractive power and aperture size.

The spectral transmittance of intraocular lenses has been previously reported.2-4 The most commonly used instrument for measuring the transmittance of ultraviolet radiation is the spectrophotometer. Although readily available and convenient to use, these instruments are better suited for transmittance measurements of a planar sample, which is unlike the intraocular lens. The principle of operation of the dual-beam spectrophotometer is based on using a collimated beam of light that has been split into two beams of equal intensity and path length. One beam serves as the reference beam while the sample of interest is inserted into the sample beam. By comparing the intensity vs wavelength of the two beams, the spectral transmittance, or absorbance, of any material can be determined. Problems arise when the sample is nonplanar, as is the case with the intraocular lens. A typical intraocular lens will have a focal length, in air, of approximately 1.5 cm. If the distance between the lens and the detector is greater than twice the lens focal length, the sample beam may expand to an area larger than the original beam. If the beam overfills the detector, then the instrument will indicate that the intraocular lens is much more absorbing than it actually is. We eliminated possible sources of error associated with the focusing properties of the lenses by using a spectroradiometer system with an integrating sphere input. This assures collection of all the radiation transmitted through the lens.

Material and Methods

Spectral transmittance measurements were performed using a double-grating spectroradiometer system interfaced to a computer. The input optics of the spectroradiometer consisted of a 3-inch (7.6-cm) diameter integrating sphere with a 4-cm² aperture. The detector was a photomultiplier tube (thermoelectrically

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cooled to -20 C), which is sensitive to optical radiation in the wavelength region from 200 to 800 nm (S-20 photocathode response).⁵ The wavelength scanning and data collection functions of the spectroradiometer were controlled by the computer. Measurements were taken every 2 nm from 250 to 400 nm, and every 5 nm from 400 to 800 nm. The spectroradiometer system was calibrated using a 1,000-W quartz halogen standard lamp that had been calibrated by the National Bureau of Standards. During our measurements, this lamp was operated by a precision power supply that was current-regulated to better than 0.025%.

Significant sources of error in the measurement process include calibration and alignment of the standard lamp (3.9%) and instrument linearity, wavelength accuracy, and repeatability of measurements (4.6%). Combination in quadrature of the above sources of error is estimated to lead to a 6% overall uncertainty in the raw data. However, when repeated trials were performed with the same intraocular lens and same input aperture on different days, the transmittance values varied by no more than 3% in the cutoff region (optical transmittance between 5% and 75%), and were in even closer agreement in the spectral region associated with optical transmittance of 75% or more.

Transmittance values were obtained by first measuring the output from the 1,000-W quartz halogen standard lamp through the empty intraocular lens holder. The lens was centrally held in place by a holder of our own design (Fig. 1). We ensured that the entire beam, both with and without the sample intraocular lens, was collected by the integrating sphere by mounting the lens holder directly in front of the sphere input aperture. The lens holder was

centered in front of the sphere input, with the limiting aperture facing the light source. This configuration was chosen to mimic the effects caused by a changing pupil size.

Using this holder, we varied the input aperture of the system to show how the outer portions of the lens, where the material is thinner, can affect the cutoff region of the transmittance curve. The intraocular lens, which rests in contact with this limiting aperture, is approximately 2 cm from the sphere input aperture. Care must be taken to ensure that the input aperture is indeed the limiting aperture of the system. We addressed this by using a retaining disk with an aperture larger than that of the holder base. The intraocular lens was held in place by the retaining disk, which has a small lip to create pressure against the lens' haptics.

The fraction of radiation transmitted was determined by dividing the radiation measured through the intraocular lens by the radiation measured through the empty lens holder. The apertures used were 1, 3, and 5 mm in diameter. We chose intraocular lens samples from four manufacturers, selecting a high-power (21 to 28 diopter) and a low-power (9 to 17 diopter) lens from each. We examined a total of six pairs of intraocular lenses, four with components alleged to be ultraviolet-absorbing and two without.

Results

There was a significant variation of ultraviolet-absorbing capability among the lenses tested. Intraocular lenses from Manufacturers 1 and 2 transmitted more than 85% of the

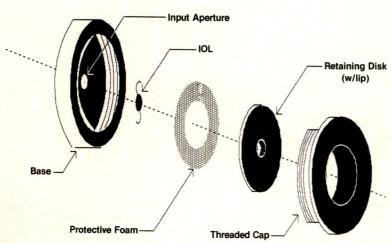


Fig. 1 (Miller and James). Intraocular lens (IOL) holder showing location of lens.

TABLE 1

PERCENT TRANSMITTANCE FOR

"ULTRAVIOLET-ABSORBING" INTRAOCULAR LENSES

THROUGH A 3-MM DIAMETER APERTURE

WAVELENGTH (NM) 425 450 390 400 LENS 380 Manufacturer 1 17.0 D 22% 69% 87% >90% >90% 21.0 D 18% 66% 87% >90% >90% Manufacturer 2 >90% 9.0 D 28% 75% 89% >90% >90% 25.0 D 11% 62% 87% >90% Manufacturer 3 87% 78% 31% 10.0 D <1% 5% 85% 71% 28.0 D <1% <1% 16% Manufacturer 4 83% 92% 3% 11.0 D <1% <1% 89% <1% 72% 25.0 D <1% <1%

incident radiation at 400 nm, whereas those from Manufacturers 3 and 4 transmitted less than 30% and 5% of the incident radiation, respectively (Table 1). Data are presented only for wavelengths of 374 nm and above because the percentage of optical radiation transmitted below 374 nm was less than 5% for the "ultraviolet-absorbing" intraocular lenses. The transmittance of the nonultraviolet-absorbing intraocular lenses from two manufacturers was similar and, as expected, they were highly transmissive above 300 nm.

We found that not only do large variations exist in ultraviolet-absorbing characteristics among different manufacturers, but also within the same manufacturer and model of intraocu-

TABLE 2
PERCENT TRANSMITTANCE FOR AN
"ULTRAVIOLET-ABSORBING" INTRAOCULAR LENS
FROM MANUFACTURER 2

WAVELENGTH	3-MM AP	ERTURE	5-MM APERTURE		
(NM)	9.0 D	25.0 D	9.0 D	25.0 D	
374	6%	<5%	9%	<5%	
376	12%	<5%	16%	5%	
378	20%	5%	24%	9%	
380	28%	11%	33%	16%	
382	39%	18%	43%	25%	
384	49%	29%	53%	36%	
386	59%	39%	61%	47%	
388	67%	55%	69%	57%	
390	75%	62%	75%	66%	
392	78%	70%	79%	74%	
394	83%	77%	83%	79%	
396	85%	82%	86%	84%	
398	88%	85%	87%	86%	
400	89%	87%	88%	88%	
404	90%	89%	88%	88%	
408	90%	>90%	89%	90%	
410-800	>90%	>90%	>90%	>90%	

lar lens when the power and aperture size are varied. The transmittance of a low-power lens is greater than that of a high-power lens because the low-power lens is thinner. In the cutoff region, the low-power lens transmitted approximately twice as much radiation as the high-power lens for Manufacturers 2 and 3. However, the transmittance values of the two lenses become equal at the wavelength of maximum transmittance (Table 2 and Fig. 2). This is demonstrated in Table 1 for ultraviolet-

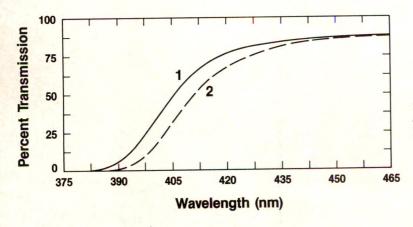


Fig. 2 (Miller and James). Transmittance curves for a low-power (1) and a high-power (2) intraocular lens from Manufacturer 3.

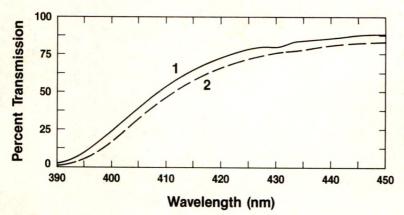


Fig. 3 (Miller and James). Transmittance curves for a 28.0-diopter lens from Manufacturer 3 through a 5-mm (1) and a 3-mm (2) aperture.

absorbing intraocular lenses, and is true for all the lenses examined in this study, both "ultraviolet-absorbing" and nonultraviolet-absorbing. Only data for the 3- and 5-mm apertures are presented in the Tables, since the measurements made with the 1-mm aperture showed, at most, a 1% variation from those made with the 3-mm aperture. This is because the thickness of the lens does not appreciably change between these two regions. Transmittance through the 5-mm aperture is slightly higher than that through the 3-mm aperture in the cutoff region (Fig. 3).

We also compared the transmittance curves of an ultraviolet-absorbing intraocular lens and a nonultraviolet-absorbing intraocular lens with that of a 53-year-old human lens (Fig. 4). Although this study was not meant to provide a comprehensive survey of a large population of lenses, none of the intraocular lenses tested matched the ultraviolet- and blue lightabsorbing capacity of the mature human lens. Since blue light is also potentially hazardous to

the retina, some investigators have suggested that an intraocular lens with a transmittance cutoff above 400 nm may be appropriate. 4,6

Discussion

Transmittance measurements were performed on 12 intraocular lenses with a standard 3- and 5-mm aperture, yielding a total of 24 different transmittance curves (measurements were also made using a 1-mm aperture on some of the lenses). The most significant results were that the transmittance of the low-power models were as much as 100% to 500% greater than that of the high-power models in the cutoff region. With the larger aperture, we typically saw a 25% to 100% difference in transmittance. Other studies have reported problems with, and possible solutions to, the use of the spectrophotometer for making transmittance measurements (unpublished data). Using a spec-

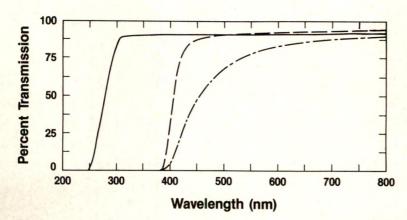


Fig. 4 (Miller and James). Transmittance curves for a nonultraviolet-absorbing intraocular lens (solid line), an ultraviolet-absorbing intraocular lens (long dashes), and a 53-year-old human lens (long and short dashes).

troradiometer with an integrating sphere eliminates the sources of error associated with the focusing properties of the intraocular lenses, and assures that all the radiation transmitted through the lens is received by the detector.

This study clearly verifies the need for standardizing the methods for measuring the ultraviolet-transmittance characteristics of intraocular lenses. One possible method that would also eliminate potential problems caused by refractive effects of the intraocular lens would be to obtain spectral transmittance curves through blanks corresponding to the thickness of the central 3 mm of the thinnest and thickest intraocular lenses. This method was one of the options suggested in the "UV-Absorbing Lens Labeling" document that the Food and Drug Administration sent to all intraocular lens sponsors in May 1986. A spectrophotometer could then be used with an air sample for reference, using the same 3-mm diameter aperture used during the lens material blank measurement. Alternatively, the spectral data could be obtained through the actual intraocular lens by techniques described in this paper.

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OPHTHALMIC MINIATURE

The healthy know not of their health, but only the sick: this is the Physician's Aphorism; and applicable in a far wider sense than he gives it. . . .

In the Body, for example, as all doctors are agreed, the first condition of complete health is, that each organ perform its function unconsciously, unheeded; let but any organ announce its separate existence, were it even boastfully, and for pleasure, not for pain, then already has one of those unfortunate "false centres of sensibility" established itself, already is derangement there. The perfection of bodily well-being is, that the collective bodily activities seem one; and be manifested, moreover, not in themselves, but in the action they accomplish.

Thomas Carlyle, "Characteristics" London, Edinburgh Review, 1831

Intraocular Lens Implantation Following Expulsive Choroidal Hemorrhage

Khalid J. Awan, M.D.

Uncomplicated posterior chamber intraocular lens implantation was performed in two eyes that had been salvaged after expulsive choroidal hemorrhage during a previous cataract operation and in one eye after loss of the fellow eye from expulsive choroidal hemorrhage. The procedure was performed in a 72year-old woman three weeks after and in an 81-year-old man four months after the successful management of expulsive choroidal hemorrhage. A third patient, an 84-year-old woman, had posterior chamber intraocular lens implantation in her remaining eye six years after the loss of other eye. All three patients had a final visual acuity of 20/40 or better after a follow-up period of six months to four years.

EXPULSIVE CHOROIDAL HEMORRHAGE is one of the most dreaded complications of intraocular surgery. Before 1915, immediate enucleation was recommended as the only management option. That year, Verhoeff² introduced posterior sclerotomy to release the suprachoroidal blood, which helped save many eyes. Today, the prognosis of expulsive choroidal hemorrhage is more favorable because of a better understanding of this condition and improvements in surgical technique and instrumentation.

Although more eyes with expulsive choroidal hemorrhage are being saved, reports of successful subsequent intraocular surgery in these eyes are rare. Herein I report the successful implantation of intraocular lenses in two eyes

that had recovered from an earlier expulsive choroidal hemorrhage and in the remaining eye of one patient who lost the fellow eye to this complication.

Case Reports

Case 1

A 72-year-old woman underwent successful extracapsular cataract extraction with posterior chamber intraocular lens implantation in her right eye. Final visual acuity was 20/20. Five months later, she underwent the same procedure in the left eye after administration of local anesthesia. The anesthetic solution was constituted by mixing 50 ml of 2% mepivacaine, 50 ml of 0.75% bupivacaine, 4 ml of 150 USP units/ml hyaluronidase, and 1.2 ml of 1:1,000 epinephrine. Three milliliters of this solution were used for retrobulbar injection and 6 ml for O'Brien facial block. When irrigation of the cortex was nearly completed, the fundus reflex suddenly darkened, the posterior lens capsule-iris diaphragm bulged forward, and the globe became hard. The irrigation/aspiration cannula was immediately removed from the anterior chamber and the preplaced sutures of 10-0 nylon in the cataract incision were quickly tied. Nevertheless, the rising pressure in the eye pushed out the knuckles of the iris between the tied sutures. The superficial scleral flap⁷ was then sutured in place over the prolapsed iris knuckles with interrupted sutures of 8-0 black silk. A posterior sclerotomy was then performed in the inferonasal quadrant about 10 mm behind the corneoscleral limbus. Only a small amount of blood was recovered, and the globe remained hard. Another posterior triangular sclerotomy was performed in the inferotemporal quadrant and a large amount of fresh blood was released, with a decrease in intraocular pressure. The anterior chamber was reformed by injection of balanced salt solution. The posterior scleroto-

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my openings were not sutured and the eye was patched. During the first postoperative night, 100 mg of intramuscular meperidine hydrochloride was required to relieve ocular pain. The next morning, visual acuity was light perception without projection and there was no fundus reflex. Nine days after surgery, visual acuity was counting fingers in two quadrants and a dark fundus reflex was visible. Ophthalmoscopic examination showed that the hemorrhage was rapidly clearing. On postoperative day 18, the fundus was clearly visible (Figure). Surgical intervention to release the iris prolapsed in the wound was thought necessary. On postoperative day 22, after administration of local anesthesia, the inferotemporal posterior sclerotomy was reopened, and the silk sutures from the scleral flap that covered the original cataract incision were removed. As each suture was removed, the prolapsed iris knuckle was freed from the wound and reposited into the anterior chamber by forced irrigation. The anterior chamber was then filled with sodium hyaluronate (Healon) and a posterior chamber intraocular lens implanted. There were no complications. A peripheral iridectomy was performed, the cataract incision closed with interrupted 10-0 nylon sutures, and the



Figure (Awan) Case 1. Eighteen days after the expulsive hemorrhage, the fundus reflex is clear. Note the incarcerated iris in the wound superiorly, and the closure of the scleral flap over the closed cataract wound in a separate row of black silk sutures. The posterior capsule and the margins of the anterior capsulotomy have formed horseshoeshaped adhesions.

Healon in the anterior chamber replaced with balanced salt solution. The postoperative course was uneventful, but the portion of the iris that had been caught in the original wound had lost much mobility. After six months, visual acuity was 20/40 and intraocular pressure was normal.

Case 2

An 81-year-old man who had undergone a successful trabeculectomy for open-angle glaucoma in his left eye two years previously was undergoing an extracapsular cataract extraction with posterior chamber intraocular lens implantation in the same eye. Local anesthesia similar to that administered in Case 1 was used. A temporal approach was used to avoid the filtering area at the 12 o'clock meridian. As the remnants of the cortical material were being cleaned from the capsular fornices, the patient moved his head, causing a sudden withdrawal of the aspiration cannula from the eye. The fundus reflex darkened, the posterior lens capsule-iris diaphragm bulged forward, the posterior capsule ruptured, and vitreous was lost from the cataract wound. The preplaced sutures were tied and a posterior sclerotomy was performed about 10 mm behind the corneoscleral limbus in the inferotemporal area, with resultant escape of a large quantity of blood. The sclerotomy opening was not sutured. The corneal wound was cleaned of the prolapsed vitreous, and the anterior chamber was reformed with balanced salt solution. Much vitreous remained in the anterior chamber. Ten days after surgery, the blood-filled fundus was visible through the clear vitreous. After 75 days, the ocular fundus was clearly visible and ocular tension was normal. Four months after the expulsive hemorrhage, using anesthesia similar to that in Case 1, the original cataract incision was opened for a thorough anterior vitrectomy. The posterior capsule, which had a tear in its center, was still in place. The anterior chamber angle was deepened with Healon in areas where iris appeared to be adherent to the cataract wound. The adhesions between the iris and the posterior capsule were also separated by injection of Healon. A posterior chamber lens was implanted without difficulty. The wound was closed, Healon aspirated, and anterior chamber reformed with balanced salt solution. The postoperative course was uneventful. Two years after surgery, intraocular pressure was 24 mm Hg, but was controlled with topical 2% pilocarpine eyedrops. Best-corrected visual acuity was 20/40.

The right eye has well-controlled glaucoma and visual acuity of 20/80 and a cataract.

Case 3

An 84-year-old woman had previously lost her left eye to an expulsive choroidal hemorrhage that occurred 16 days after intracapsular cataract extraction. She refused cataract surgery for the right eye until six years later. After administration of local anesthesia, extracapsular cataract extraction and posterior chamber intraocular lens implantation was performed. There were no complications. Before making the cataract incision, as a prophylactic measure, a triangular scleral flap for a posterior sclerotomy in the inferotemporal quadrant was prepared 10 mm behind the corneoscleral limbus. Four years after surgery, uncorrected visual acuity was 20/40.

Discussion

Although several studies on the pathogenesis and management of expulsive choroidal hemorrhage have been recently reported, 9-13 it is still not possible to know which patients are at risk. Patients who are elderly or have arteriosclerosis, hypertension, diabetes mellitus, blood dyscrasias, glaucoma, severe myopia, choroidal sclerosis, and a history of expulsive hemorrhage are considered at risk. 13 A family history of systemic vascular disease may also be considered a risk factor. The intraoperative factors that may contribute to the development of excessive bleeding include sudden decrease of intraocular pressure, increased cephalic venous pressure as in the Valsalva maneuver and coughing, vitreous loss, sudden rise in systemic blood pressure, and administration of retrobulbar anesthesia without epinephrine.13 In most of my patients who developed expulsive hemorrhage (six cases), the intraocular operative manipulation was more prolonged than

The most important factors in the successful management of expulsive choroidal hemorrhage are early recognition, quick closure of the incision, and exteriorization of the suprachoroidal bleeding through a sclerotomy opening. Properly executed posterior sclerotomies are important in limiting intraocular damage.

It is encouraging that more eyes are being salvaged after expulsive choroidal hemorrhage. The cases reported here show that intraocular surgery in such eyes is possible and provides good vision. The patients must be thoroughly examined preoperatively and precautionary measures, such as reduction of the intraocular pressure, reopening of the original posterior sclerotomies or creating new ones before opening the eye, preplacing the sutures, and making a small but adequate incision, be implemented. With these precautions, a repeated intraocular procedure on an eye that has been saved from a previous expulsive choroidal hemorrhage may be safely carried out.

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Pseudophakic Bullous Keratopathy

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We reviewed the records of all patients with pseudophakic bullous keratopathy (271 eyes, 251 patients) seen during a six-month period to determine predisposing factors, associated problems, current management, and visual outcome. Pseudophakic bullous keratopathy was associated most frequently with anterior chamber intraocular lenses in general (155 of 271), and with Leiske style lenses in particular (100 of 271). It was associated with a visual acuity of 20/200 or less in 206 eyes and a visual acuity of counting fingers or less in 129 of the eyes at the initial examination. Penetrating keratoplasties had been performed in 189 of the eyes. After penetrating keratoplasty, 108 of 189 of the eyes had a visual acuity of 20/200 or less (mean follow-up, 15 months). Visual acuity improved with longer follow-up, and among patients with a minimum follow-up of two years, 23 of 36 eyes had a visual acuity of 20/100 or better. Most grafts were clear (145 of 189). Pseudophakic bullous keratopathy was associated with marked visual loss, which was permanent despite clear grafts in 29 of 92 eyes followed-up for one year or longer.

PSEUDOPHAKIC BULLOUS KERATOPATHY, which is associated with marked visual loss, is currently the most common indication for penetrating keratoplasty. Recently, a number of authors have described the results of corneal transplantation and discussed various approaches to the intraoperative management of the intraocular lens. Per We undertook this study to define the magnitude of this disease in a referral cornea practice in patients who have

and have not undergone penetrating keratoplasty. We analyzed the pattern of associated intraocular lenses and ocular problems as well as results following penetrating keratoplasty with regard to the type and management of the intraocular lens to determine factors influencing graft clarity and visual acuity.

Material and Methods

We reviewed the outpatient records of all private patients seen on the Cornea Service at our institution with a diagnosis of pseudophakic bullous keratopathy during a six-month period beginning Sept. 15, 1986. Patients seen for the first time and patients seen in follow-up with this diagnosis were included. Medical records were analyzed to determine the type of intraocular lens, the onset of edema by history, and visual acuity at the time of referral, before penetrating keratoplasty, and when last examined. Information was also collected regarding patients in this series who had undergone penetrating keratoplasty. The operative management of the intraocular lens was correlated with the outcome in terms of graft clarity and visual acuity. An effort was made to determine other factors contributing to poor visual acuity, including cystoid macular edema and glaucoma.

Results

The study included 271 eyes (251 patients). The mean age was 75 years (range, 58 to 93 years). Of the 271 cases of pseudophakic bullous keratopathy, 166 occurred in women. Cataract surgery had been performed in all patients between 1973 and 1986. Information regarding the technique of cataract extraction was incomplete in many records. A secondary

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intraocular lens had been inserted in 26 of the eyes. Information regarding intraoperative and postoperative complications of the cataract surgery and intraocular lens implantation was frequently unavailable.

Pseudophakic bullous keratopathy was associated with anterior chamber intraocular lenses in 155 of 271 eyes. Iris-fixated intraocular lenses were present in 65 eyes, and posterior chamber intraocular lenses were present in 36 eyes. In 15 eyes, the type of intraocular lens could not be determined from the records because the lens had been explanted before referral.

Leiske style intraocular lenses accounted for 100 of 155 of the anterior chamber lenses and were the most common type of lens in this series. The remaining anterior chamber lenses included Azar (eight), Kelman II (nine), Choyce (eight), and Multiflex (four). The most common types of iris-fixated lenses were Binkhorst two-and four-loop iris clip lenses (27 of 65) and Copeland lenses (28 of 65). The type of posterior chamber lens was unknown or not specified in most cases.

The onset of edema after cataract surgery was described in 140 of 271 of the records at an average interval of 24 months. The average onset of edema was earliest in eyes with posterior chamber lenses (four months), latest in eyes with iris-fixated intraocular lenses (47 months), and intermediate in eyes with anterior chamber lenses (24 months). Among eyes with posterior chamber intraocular lenses in which information was available, 14 of 23 developed irreversible corneal decompensation immediately after cataract surgery.

At the time of initial examination, visual acuity was 20/200 or less in 206 of 271 eyes and counting fingers or less in 129 of those eyes.

Penetrating keratoplasties had been performed in 189 of 271 eyes, including 99 with anterior chamber, 58 with iris-fixated, and 24 with posterior chamber intraocular lenses as well as eight with an unknown type of lens. Preoperative visual acuity was 20/200 or less in 165 of 189 eyes. Many of the patients who had not undergone penetrating keratoplasty were on the waiting list to receive a graft at the close of the study. Other patients were not candidates for surgery because visual acuity in the fellow eye was good and their affected eye was not painful. Some patients were not candidates for corneal transplantation because of the presence of other significant ocular diseases, including glaucoma, retinal detachment, and cystoid macular edema. Of 271 eyes, 35 had a history of glaucoma and 26 had a history of cystoid macular edema. Seven eyes had a history of retinal detachments and five had been treated for corneal ulcers.

Clear grafts were achieved in 145 of 189 eyes after one graft. Of the 44 eyes with failed grafts, 19 underwent repeat penetrating keratoplasties. Leiske style (nine) and Copeland style (four) intraocular lenses were most commonly associated (13 of 19) with repeat grafts. All but one of these lenses had been retained at the time of the first transplant. The repeat graft was successful in 12 of 19 eyes. Three additional clear grafts were obtained after a third penetrating keratoplasty.

The visual acuity results varied depending on the duration of follow-up. Overall, after an average follow-up period of 15 months, only 24 of 170 eyes achieved a visual acuity of 20/40 or better, and 107 of 170 had a visual acuity of 20/200 or less. There was evidence of improving visual acuity in 83 of 170 eyes followed up for one year or longer after one graft (Table 1). Although the numbers are small after a follow-up period of two years or longer, 11 of 36 eyes had a visual acuity of 20/40 or better and 23 of 36 had a visual acuity of 20/100 or better. Visual acuity was better among eyes followed up for two years or longer than among eyes followed up for 12 to 23 months (Table 1).

The outcome also varied with the type of intraocular lens. Of 24 eyes with posterior chamber intraocular lenses, 22 had a clear graft and 15 attained a visual acuity of 20/100 or better during a follow-up period averaging 11 months. Of 63 eyes with Leiske style intraocular lenses, 15 had a visual acuity of 20/100 or better after an average follow-up period of ten

TABLE 1
VISUAL ACUITY IN EYES WITH ONE PENETRATING
KERATOPLASTY AFTER 12 OR MORE MONTHS

	12-2	23 MOS	≥24 MOS	
VISUAL ACUITY*	NO.	(%)	NO.	(%)
20/20 to 20/40	5	(11)	11	(31)
20/50 to 20/100	10	(21)	12	(33)
20/200 to 20/400	15	(32)	7	(19)
CF to HM	16	(34)	5	(14)
LP to NLP	1	(2)	1	(3)
Total	47	(100)	36	(100)

^{*}CF, counting fingers; HM, hand motions; LP, light perception; NLP, no light perception.

TABLE 2
VISUAL ACUITY AFTER PENETRATING KERATOPLASTY
BY TYPE OF INTRAOCULAR LENS

		TERIOR AMBER	LEISKE	
VISUAL ACUITY*	NO.	(%)	NO.	(%)
20/20 to 20/40	3	(12)	4	(6)
20/50 to 20/100	12	(50)	11	(18)
20/200 to 20/400	6	(25)	24	(38)
CF to HM	3	(13)	24	(38)
Total	24	(100)	63	(100)

^{*}CF, counting fingers; HM, hand motions.

months, even though 51 of 63 eyes had a clear graft (Table 2).

The fate of the intraocular lens was correlated with the type of intraocular lens and the year of surgery (Table 3). Posterior chamber intraocular lenses were almost always (23 of 25) left in place, iris-fixated lenses were left in place (21 of 58) or exchanged (26 of 58) with approximately equal frequency, and anterior chamber lenses were left in place (56 of 93) twice as often than they were exchanged (27 of 93). When intraocular lenses were exchanged, an open-loop Kelman Multiflex anterior chamber lens was used. The management of the anterior chamber intraocular lenses shifted with time. In 1985, 25 of 32 of the anterior chamber intraocular lenses were left in place and only six of 32 were exchanged. By 1986, 17 of 38 of the anterior chamber lenses were left in place, 11 of 38 were exchanged, and the remainder were removed at the time of (five of 38) or before (five of 38) penetrating keratoplasty.

The graft outcome was correlated with the management of the intraocular lens. After one graft, 22 of 44 failures occurred when an anterior chamber lens was left in place. The failure rate for grafts with retained anterior chamber lenses was higher (22 of 56) than for the population as a whole (44 of 189). The graft failure rate in eyes with retained iris-fixated intraocular lenses (eight of 21) was similar to that associated with retained anterior chamber intraocular lenses. The graft failure rate was low among eyes with retained posterior chamber intraocular lenses (two of 25) and following intraocular lens exchange (five of 53) and moderate in eyes in which the intraocular lens was removed before or at the time of surgery (seven of 33).

TABLE 3
MANAGEMENT BY TYPE OF INTRAOCULAR LENS

MANAGEMENT	IRIS- FIXATED	ANTERIOR CHAMBER	POSTERIOR CHAMBER	TOTAL
Left in	21	56	23	100
Exchanged	26	27	0	53
Removed	11	9	0	20
Repositioned	0	1	2	3
Total	58	93	25	176*

^{*}Thirteen lenses were removed before penetrating kerato-plasty.

The results for pseudophakic bullous keratopathy associated with Leiske style intraocular lenses were analyzed separately because this was the most common type of lens used in this series. During a follow-up period averaging ten months, the graft failure rate was low (12 of 62). The failure rate was six times higher in eyes with retained Leiske intraocular lenses (ten of 34) than in those with exchanged intraocular lenses (one of 21). The difference in visual acuity was less between eyes with retained and those with exchanged Leiske lenses. Eight of 34 eyes with retained lenses and six of 21 eyes with exchanged lenses had a visual acuity of 20/100 or better. Of 34 eyes with retained lenses, 17 had a visual acuity of counting fingers or less, whereas 11 of 21 eyes with exchanged lenses had a visual acuity of 20/200 to 20/400.

Discussion

Pseudophakic bullous keratopathy was a common corneal problem, with over 250 patients seen in the course of this six-month study. Most recent reports describe the results of corneal transplantation for this indication. 2-21 The extent of the problem is underestimated if patients who have not undergone penetrating keratoplasty are not included. In this series, almost one third of the patients had not had grafts for a variety of reasons. Some patients were on the graft list, others were not interested in surgery because they had good vision in their other eye and were comfortable in the affected eye, and some were known to have poor visual potential because of other ocular problems that preceded the development of corneal decompensation.

This series of a large group of eyes with pseudophakic bullous keratopathy that have undergone penetrating keratoplasty enables comparison to previous reports and conclusions regarding changing trends in the nature and management of this increasingly common problem. The intraocular lenses reported in association with pseudophakic bullous keratopathy can be correlated with trends in intraocular lens implantation in the United States.²² Iris-fixated intraocular lenses have not been implanted since 1982, the same year that anterior chamber lenses peaked in popularity. In 1982, anterior and posterior chamber lenses were implanted with approximately equal frequency. Since that time, the use of posterior chamber lenses has increased and accounted for 86% of all lenses by 1986, with the remainder being anterior chamber lenses. Analogously, the initial reports regarding penetrating keratoplasty for pseudophakic bullous keratopathy described patients with iris-fixated intraocular lenses.2-10 More recently, reports described patients with both iris-fixated and anterior chamber intraocular lenses. 11-18 Only in the past year have there been series reported of patients with posterior chamber intraocular lenses and corneal decompensation. 19,20 In our study, anterior chamber intraocular lenses were most common but problems associated with iris-fixated lenses persisted and the frequency of problems with posterior chamber intraocular lenses was rising.

Changing trends regarding the management of pseudophakic bullous keratopathy need to be analyzed, taking into account the types of implants involved. Between 1978 and 1984, removal or retention of the intraocular lens was considered not to affect the prognosis, and lenses were left in place if they were well positioned and not associated with other complications. During that time, a number of reports dealt with patients with predominantly iris-fixated intraocular lenses who required penetrating keratoplasty for pseudophakic bullous keratopathy.2-10 Retention or removal of the intraocular lens did not appear to influence the prognosis. 3,5,9 Visual acuity was significantly better in one series with retained intraocular lenses,6 and in another series, it was worse following intraocular lens removal.7 The consensus was that the intraocular lens should be left in place if it was well positioned and not associated with chronic inflammation. 6,7 Despite high rates of graft clarity, the final visual acuity was often disappointing.8

By 1984 and 1985, authors began describing patients with anterior and posterior chamber lenses as well as iris-fixated lenses who had pseudophakic bullous keratopathy. The option of intraocular lens exchange was added to the choices of intraocular lens removal and retention. In 1984, Kozarsky and associates11 included patients with posterior chamber lenses and noted improved visual acuity results in these patients. Intraocular lens retention was then recommended. The results following lens retention, removal, and exchange were reported to be similar, although there was a tendency for eyes with retained lenses to have better visual acuity. 12,13 It is noteworthy that iris clip and Stableflex anterior chamber lenses were used for exchange in these patients in view of subsequent information regarding complications with the latter lens.23

Concern regarding retention of irissupported and anterior chamber lenses was evident by 1985. Increased endothelial cell loss was documented in patients with retained compared to removed iris-supported and anterior chamber lenses. ¹⁴ Retained anterior chamber intraocular lenses were associated with the worst prognosis and posterior chamber lenses with the best outcome. ¹⁵

In 1987, problems with closed-loop semiflexible anterior chamber intraocular lenses were stressed in the literature. 16-18,22,23 Despite high rates of graft clarity, the visual outcome was often disappointing. 16-18 Removal of irissupported lenses and closed-loop anterior chamber lenses, which were associated with frequent complications, was recommended. 18

Most recently, reports of series with posterior chamber lenses have been published. ^{19,20} The visual results have been favorable with these lenses. Corneal decompensation is frequently associated with preexisting endothelial dystrophy when it occurs after extracapsular cataract extraction and posterior chamber intraocular lens implantation. ^{20,24} Endothelial dystrophy is a risk factor for early corneal decompensation following cataract surgery that is unrelated to the intraocular lens.

In another series that included patients who underwent corneal transplantation for pseudophakic bullous keratopathy between 1980 and June 1, 1985, with a minimum of one year of follow-up, a high graft failure rate was associated with retained anterior chamber lenses. ²¹ The data supported the recommendation that closed-loop anterior chamber lenses and Copeland iris-supported lenses be removed

and that posterior chamber lenses be retained. Our larger series with more variable follow-up provides additional data supporting these conclusions.

In this series, the early onset (average, four months) of corneal decompensation with posterior chamber intraocular lenses, the late onset (average, 47 months) with iris-fixated lenses, and intermediate onset (average, 24 months) with anterior chamber intraocular lenses has implications regarding the pathogenesis of corneal decompensation associated with different intraocular lenses. Preexisting endothelial dystrophy is a factor predisposing to early corneal decompensation in some patients undergoing extracapsular cataract extraction and posterior chamber lens implantation. 20,24 The earlier onset of edema associated with anterior chamber lenses compared to iris-fixated lenses suggests that inflammation associated with anterior chamber lenses may be greater than with iris-fixated lenses. In retrospect, the shift from iris-fixated lenses to closed-loop anterior chamber lenses may not have been a sign of prog-

Prolonged follow-up is necessary after corneal transplantation in general but in particular in patients with pseudophakic bullous keratopathy. Long-term follow-up has documented increasing graft failure in patients with retained closed-loop anterior chamber implants.21 Our data show, however, that visual acuity gradually improves over a period of several years. Patients with posterior chamber lenses experience more rapid and complete visual rehabilitation. Our data are encouraging regarding graft clarity following intraocular lens exchange using open-loop Kelman Multiflex lenses, although the visual acuity results are not comparable to those achieved in patients with posterichamber intraocular lenses. Longer follow-up in more patients is needed to determine the prognosis for intraocular lens exchange using open-loop anterior chamber lenses or sutured posterior chamber lenses at the time of keratoplasty in patients with closedloop anterior chamber and iris-fixated lenses.

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OPHTHALMIC MINIATURE

That, as the creative state of the eye increased, a sympathy seemed to arise between the waking and the dreaming states of the brain in one point—that whatsoever I happened to call up and to trace by a voluntary act upon the darkness was very apt to transfer itself to my dreams; so that I feared to exercise this faculty; for, as Midas turned all things to gold, that yet baffled his hopes and defrauded his human desires, so whatsoever things capable of being visually represented I did but think of in the darkness, immediately shaped themselves into phantoms of the eye; and, by a process apparently no less inevitable, when thus once traced in faint and visionary colors, like writings in sympathetic ink, they were drawn out by the fierce chemistry of my dreams, into insufferable splendor that fretted my heart.

Thomas De Quincey, Confessions of an English Opium-Eater London, London Magazine, 1821

Endothelial Function and Aqueous Humor Flow Rate in Patients With Fuchs' Dystrophy

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Using a two-dimensional scanning fluorophotometer, we studied 50 subjects with symmetric ocular involvement of Fuchs' dystrophy without epithelial edema. Twenty-six subjects with confluent or nearly confluent cornea guttata with increased corneal thickness and 24 subjects with mild to moderate cornea guttata with normal corneal thickness were compared to normal control subjects. There were no statistically significant differences in endothelial permeability between the three groups. Corneal thickness was significantly increased in the subjects with confluent to nearly confluent guttae, however. These results suggest that endothelial pump function may be affected in subjects with advanced cornea guttata with stromal edema.

FUCHS' DYSTROPHY is a progressive disorder of the corneal endothelium characterized by a decrease in the number and function of endothelial cells. Clinically, the disease is characterized by the appearance of small drop-like excrescences (guttae) in Descemet's membrane, a condition termed cornea guttata. Ultimately, stromal and epithelial edema may occur, resulting in severe visual loss. The origin of the disease is unknown.

We undertook the present study to assess endothelial function in Fuchs' dystrophy using the two-dimensional scanning ocular fluorophotometer. We also investigated the rate of flow of aqueous humor in Fuchs' dystrophy.

Patients and Methods

We recruited 50 patients with stage 1 (no epithelial edema) Fuchs' dystrophy and relatively symmetric ocular involvement. Twentysix of the patients had confluent or nearly confluent guttae (21 confluent, five nearly confluent) and 24 had mild to moderate guttae (Fig. 1). We also recruited 41 control subjects without ocular disease except for cataract. We obtained a complete ocular history from all participants and performed a physical examination, including biomicroscopy with a slit lamp and a Hruby lens, indirect ophthalmoscopy, and Goldmann tonometry. We measured background fluorescence of the cornea and





Fig. 1 (Wilson and associates). Representative endothelial specular micrographs of patients with Fuchs' dystrophy with confluent or nearly confluent guttae (top) and mild to moderate guttae (bottom).

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anterior chamber with a two-dimensional scanning fluorophotometer.2 All subjects had clear corneal stroma and no epithelial edema. All subjects had an initial intraocular pressure in both eyes of less than or equal to 22 mm Hg. No subject had extraocular or intraocular inflammation (no conjunctival injection, no inflammatory cells in the cornea on slit-lamp examination, and less than one cell per 1 × 2-mm slit-lamp beam in the anterior chamber). No subject was taking ocular medications such as beta-receptor blockers or agonists, antiinflammatory medications, or oral carbonic anhydrase inhibitors for at least two weeks before the start of the study. None of the subjects had previous ocular surgery or ocular abnormalities other than cataract. We obtained detailed informed consent from each participant.

At 4 A.M. on the first day of the study, each subject administered one drop of 2% fluorescein in each eye, followed by a second drop five minutes later. The subject was instructed to remove excess fluorescein from the eyelids with a moist cottonball and return to sleep. We measured fluorescein concentration in the corneal stroma and anterior chamber with the two-dimensional scanning fluorophotometer at 10 A.M., 11 A.M., 12 noon, 1 P.M., and 2 P.M. Between measurements, the subjects were permitted to participate in their normal activities. The subjects were instructed to refrain from drinking alcohol or large volumes of water, using any drugs, or eating large meals, any of which might alter anterior chamber aqueous humor dynamics.

We instilled another drop of 2% fluorescein in both eyes in most patients from all three groups after the 2 P.M. measurement, when corneal and anterior chamber fluorescein concentrations had decayed to lower levels. After ten minutes, we repeated measurements of fluorescein concentration in the corneal stroma and anterior chamber. The ratio of the change in anterior chamber fluorescein concentration to the change in corneal stroma fluorescein concentration over the ten-minute period was determined for each eye; this was referred to as the optical boundary function.3 Ten minutes after this application of fluorescein, little if any of the applied fluorescein would have reached the anterior chamber. Increased optical boundary function in the patients with Fuchs' dystrophy compared with normal controls would indicate a false increase in the measured anterior chamber fluorescein concentration caused by fluorescein in the thicker stroma. Polarization

of fluorescence measurements of the cornea and anterior chamber were made for all subjects. We then measured corneal thickness with a Heyer-Schulte specular microscope.

We calculated endothelial permeability and aqueous humor flow rate using previously published methods. 5,6 Endothelial permeability to fluorescein was determined from the rate of disappearance of fluorescein from the cornea and the gradient between the stroma and the anterior chamber. The cornea-to-anterior chamber mass transfer coefficient (k_{e-ca}) was calculated using equations derived from those of Jones and Maurice, assuming the stroma-to-anterior chamber distribution ratio of fluorescein at equilibrium (r_{ca}) in humans is 1.6. We calculated endothelial permeability to fluorescein in centimeters per minute as follows.

permeability =
$$k_{e-ca} \times CT \times r_{ca}$$
,

where $k_{\text{c-ca}}$ is the mean of the values calculated for each of the four hourly intervals and CT is the central corneal thickness in millimeters as measured with the specular microscope. The volume of corneal stroma was assumed to be 70 μ l for corneas with a central thickness of 0.55 mm, the average thickness found in normal subjects measured with the same specular microscope. We then calculated corneal volume for each subject using the following equation to adjust for corneal thickness:

corneal volume in $\mu l = CT/0.55 \times 70 \mu l$.

Anterior chamber volume was determined by using a photogrammetric method. 10

Since subjects with relatively symmetric corneal involvement were studied, values from the two eyes for endothelial permeability, aqueous humor flow rate, polarization of fluorescence in the stroma, polarization of fluorescence in the anterior chamber, and optical boundary function were averaged to give a single value for each parameter for each subject.

In seven patients with Fuchs' dystrophy and six normal controls, endothelial permeability and aqueous humor flow rate were measured on five separate occasions, a minimum of five days apart. We selected subjects for multiple measurements so that individuals with both normal and relatively low aqueous humor flow rates on the first measurements were present in each group.

Statistical comparisons were performed by using a standard Student's t-test for unpaired

data. $P \le .05$ was considered significant. Additionally, data on aqueous humor flow rate and endothelial permeability for the Fuchs' dystrophy and control subjects were compared by means of an extension of the t-test for situations in which patients respond differentially to disease, 11 for example, the effect of flow rate on the disease varies from patient to patient. The standard test assumes that if patients with Fuchs' dystrophy have a diminution in flow rate, the magnitude of the diminution is the same in every patient. The mathematical implication of this assumption is as follows. Let Y equal the log odds of the probability that a person has Fuchs' dystrophy. If one were to graph Y against flow rate (X), the standard t-test assumes that the plot would be a straight line (which would have zero slope if there were no association between flow rate and disease and a nonzero slope otherwise). The observed relationship in this study was significantly nonlinear (P = .007). Therefore, we used the generalized t-test, which allows for the possibility that the relationship may be nonlinear.

Results

Table 1 contains means and standard deviations for all of the measured and calculated values for the normal subjects, subjects with mild to moderate guttae, and subjects with confluent to nearly confluent guttae. In one control subject and one subject with mild to moderate guttae, calculations for endothelial permeability and aqueous humor flow rate were not possible for one eye because of inad-

vertent transfer of fluorescein into the eye from the eyelids during fluorophotometry. Therefore, data for these subjects were not used for statistical computations involving these variables. Corneal thickness (Fig. 2) was higher in subjects with advanced cornea guttata compared with subjects with early cornea guttata or control subjects. Mean endothelial permeability (Fig. 3) was similar in the three groups. The range of values tended to be greater, however, in subjects with cornea guttata. Mean aqueous humor flow rates were also similar for the three groups (Fig. 4). Again, however, the range of aqueous humor flow rates was greater for subjects with either advanced or early cornea guttata compared with control subjects.

In a comparison between the normal subjects and subjects with mild to moderate guttae or confluent to nearly confluent guttae, there was no statistically significant difference between the normal subjects and subjects with mild to moderate cornea guttata for any of the measured variables (Table 2). There was also no statistically significant difference between the normal subjects and subjects with confluent to nearly confluent guttae in endothelial permeability, aqueous humor flow rate, fluorescence polarization of the corneal stroma, or optical boundary function. Statistically significant differences were noted between controls and subjects with confluent to nearly confluent guttae in corneal thickness and fluorescence polarization in the aqueous humor. Corneal thickness and fluorescence polarization in the aqueous humor were increased in subjects with confluent to nearly confluent guttae compared with controls. Mean and range of intraocular pressure were not statistically significantly different

TABLE 1
MEANS OF MEASURED VARIABLES*

NO. OF GROUP SUBJECTS				ENDOTHELIAL	AQUEOUS HUMOR	FLUORESCENCE POLARIZATION		OPTICAL
	AGE THICKNESS (YRS) (MM)	PERMEABILITY TO FLUORESCEIN (×10 ⁻⁴ cm/min)	FLOW RATE (µL/MIN)	CORNEAL STROMA	AQUEOUS HUMOR	BOUNDARY FUNCTION		
Normal 41	63.2	0.57	4.27	2.52	0.1655	0.0341	0.023	
		(12.7)	(0.03)	(0.74)	(0.47)	(0.0247)	(0.0139)	(0.011)
Mild to moderate	24	69.2	0.56	4.32	2.35	0.1700	0.0364	0.026
cornea guttata		(10.2)	(0.02)	(1.04)	(0.58)	(0.0254)	(0.0152)	(0.007)
Confluent to nearly	26	61.6	0.59	4.45	2.52	0.1661	0.0469	0.025
confluent cornea guttata		(14.4)	(0.03)	(1.14)	(0.83)	(0.0249)	(0.0237)	(0.011)

^{*}Numbers in parentheses are standard deviations.

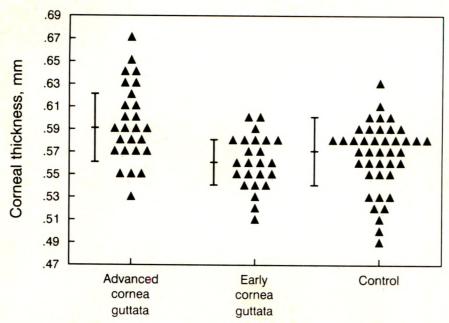


Fig. 2 (Wilson and associates). Corneal thickness in patients with confluent to nearly confluent cornea guttata (advanced) and mild to moderate cornea guttata (early) and in normal control subjects. Bars represent the mean ± 1 S.D.

between subjects with confluent to nearly confluent cornea guttata (mean \pm S.D., 14.5 \pm 3.1 mm Hg; range, 10 to 22 mm Hg), subjects with mild to moderate cornea guttata (15.8 \pm 2.8 mm Hg; range, 10 to 22 mm Hg), and controls (15.6 \pm 2.8 mm Hg; range, 8 to 22 mm Hg).

The distribution of aqueous humor flow rate for subjects with cornea guttata (Fig. 4) suggests either that flow is more variable in these patients or that the procedure for measuring flow is less reliable (generalized t-test, $P = .02^{11}$). If the measurement is affected by scatter-

ing of light or nonuniform distribution of fluorescein in the abnormal cornea, the increased variability of flow in the two groups can be interpreted as increased error of measurement. If accuracy of the test is not affected by the corneal abnormalities, the distribution suggests that an abnormality of aqueous humor flow can accompany cornea guttata. There is no statistically significant evidence of differences in distribution with respect to endothelial permeability when the normal controls are compared to either the subjects with confluent to

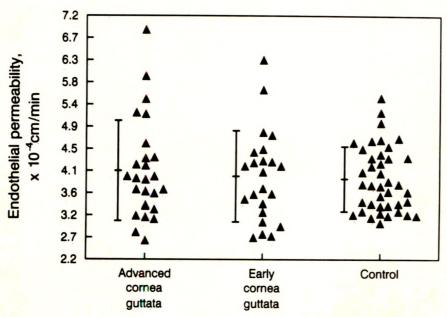


Fig. 3 (Wilson and associates). Endothelial permeability in patients with confluent to nearly confluent cornea guttata (advanced) and mild to moderate cornea guttata (early) and in normal control subjects. Bars represent the mean ± 1 S.D.

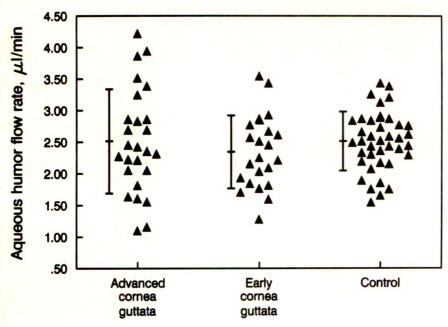


Fig. 4 (Wilson and associates). Aqueous humor flow rate in patients with confluent to nearly confluent cornea guttata (advanced) and mild to moderate cornea guttata (early) and in normal control subjects. Bars represent the mean \pm 1 S.D.

nearly confluent guttae (P = .09) or all subjects with guttae (P = .07). Generalized two-sided *t*-test comparisons for endothelial permeability between these pairs, P = .17 and P = .16, respectively, are not significant.

By the method of Lachin,¹² a similar study would be expected to find a statistically significant difference in endothelial permeability between normal control subjects and subjects with confluent to nearly confluent guttae, with 90% certainty if the true difference were at least $0.92 \times 10-4$ cm/minute or 22% (two-sided non-paired analysis, alpha = 0.05, beta = 0.10,

TABLE 2
STATISTICAL COMPARISONS BETWEEN THE FUCHS'
DYSTROPHY SUBGROUPS AND NORMAL CONTROL
SUBJECTS*

VARIABLE	MILD TO MODERATE GUTTAE	CONFLUENT TO NEARLY CONFLUENT GUTTAE		
Corneal thickness	.30	.001		
Endothelial permeability	.80	.45		
Aqueous humor flow rate	.21	.94		
Fluorescence polarization, stroma	.51	.89		
Fluorescence polarization, aqueous humor	.56	.01		
Optical boundary function	.38	.69		

^{*}All values represent P values for a standard two-sided Student's t-test.

standard deviation used was that of normal subject group).

Since fluorescence polarization in the aqueous humor was statistically significantly increased in subjects with confluent to nearly confluent guttae compared with normal controls, correlation coefficients were calculated between fluorescence polarization in the aqueous humor and the other variables in Table 1 for the subjects with confluent to nearly confluent guttae. There were no statistically significant correlations.

Endothelial permeability and aqueous humor flow rates for an individual eye appeared to remain stable over time (Figs. 5 and 6). For an individual subject, endothelial permeability and aqueous humor flow rate tended to be similar in the right and left eye. The clustering of either measurement for an individual eye also confirms the precision of the measurement of endothelial permeability and aqueous humor flow rate obtained with the two-dimensional scanning ocular fluorophotometer.

Discussion

In the present study, performed with the two-dimensional scanning fluorophotometer, we found no difference in endothelial permeability between normal subjects and subjects with Fuchs' dystrophy with increased central

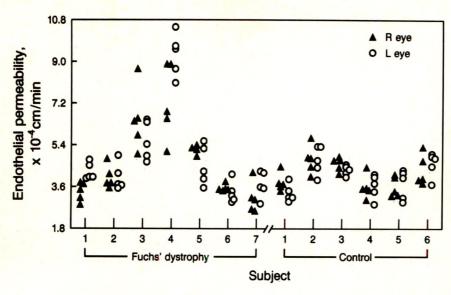


Fig. 5 (Wilson and associates). Multiple measurements, separated by at least five days, of endothelial permeability in the right and left eyes of seven patients with cornea guttata and six normal control subjects.

corneal thickness without epithelial edema. Since corneal thickness is determined by the relationship between endothelial permeability and endothelial pump rate, these results suggest that the endothelial pump rate is decreased in these patients with confluent to nearly confluent cornea guttata.

Three studies have reported increased endothelial permeability in patients with central cornea guttata without epithelial edema. Stanley¹³ calculated water permeability of human corneal endothelium by monitoring the rate of corneal thinning in response to perfusion of the epithelial surface with hypertonic solutions. He reported a 53% increase in endotheli-

al permeability in three patients with normal corneal thickness and central cornea guttata without epithelial edema compared with three normal subjects. Waltman and Kaufman, 14 in studying endothelial permeability to fluorescein using the slit-lamp fluorophotometer, found no correlation between the clinical appearance of cornea guttata and endothelial permeability to fluorescein. Two of their patients with cornea guttata and normal corneal thickness, however, were found to have increased endothelial permeability to fluorescein compared to normal subjects. Two of our patients with cornea guttata also had endothelial permeabilities that were higher than any of those in the control

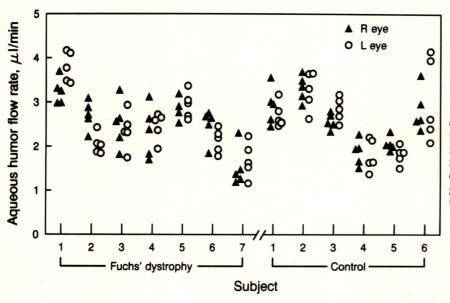


Fig. 6 (Wilson and associates). Multiple measurements, separated by at least five days, of aqueous humor flow rate in the right and left eyes of patients with cornea guttata and six normal control subjects.

subjects (Fig. 3). In neither of these previous studies was the difference in endothelial permeability between patients with cornea guttata and normal subjects evaluated statistically.

Burns, Bourne, and Brubaker, ¹⁵ using the slit-lamp fluorophotometer, compared 21 patients with prominent cornea guttata without epithelial edema to 17 age- and sex-matched normal controls. A statistically significant increase in the mean endothelial permeability was found in the patients with Fuchs' dystrophy. The calculated mean endothelial pump rate did not differ between the two groups. These last results suggested that a breakdown in endothelial barrier function was the earliest defect that occurred in Fuchs' dystrophy.

Patients with confluent to nearly confluent guttae in the present study were comparable in the extent of disease to subjects in the Burns, Bourne, and Brubaker study. The present study is larger, and subjects with mild to moderate cornea guttata were also studied. The present study was also performed with the precise two-dimensional scanning fluorophotometer, and five measurements of stromal and anterior chamber fluorescein concentration were used to calculate the endothelial permeability for a subject on a particular day instead of three. Figures 5 and 6 demonstrate the precision of the measurements with the two-dimensional scanning fluorophotometer and the relative consistency of these measurements over time for a particular normal subject or a subject with Fuchs' dystrophy.

It must be emphasized that absolute values of endothelial permeability obtained using the slit-lamp fluorophotometer and the twodimensional scanning fluorophotometer are not directly comparable. Mean endothelial permeability to fluorescein determined for control subjects by using the slit-lamp fluoro-photometer in the Burns, Bourne, and Brubaker study¹⁵ (2.89 \times 10⁻⁴ cm/min) was comparable to that found using the same instrument in a study of 112 normal subjects16 (2.4 × 10⁻⁴ cm/min). Similarly, mean endothelial permeability to fluorescein for control subjects in the present study determined with the twodimensional scanning fluorophotometer (4.27 \times 10⁻⁴ cm/min) is similar to that found with the same instrument in a study of 80 normal subjects⁶ (4.03 \times 10⁻⁴ cm/min). Any conclusions regarding changes in endothelial permeability must, therefore, be based on concurrent control subjects, regardless of which technique is

Explanations for finding no difference in endothelial permeability by using a more precise measurement when a difference has been previously found with a less precise method include the possibility of a type I error in the Burns, Bourne, and Brubaker study. This would be expected to occur 5% of the time. Alternatively, differences between the studies may reflect variability between Fuchs' dystrophy patients in the different studies. Whatever the correct explanation, the present study suggests that increased endothelial permeability is not an invariable finding in patients with cornea guttata and increased corneal thickness.

Data in the present study suggesting that endothelial permeability is normal in patients with Fuchs' dystrophy without epithelial edema and that pump function, therefore, diminishes with progression of the disease must, however, be viewed with caution. Several assumptions that may not be valid are inherent in the methods used to reach this conclusion. We assumed that the cornea-to-anterior chamber distribution ratio (r_{ca}) , used in the calculation of endothelial permeability, is the same in normal subjects and patients with Fuchs' dystrophy. Whether this is true or not is unknown. The fluorescence of fluorescein in the corneal stroma is known to be quenched to a certain extent compared to fluorescence in water, 17,18 although the mechanism for the phenomenon is unknown. Whether this quenching effect is different in normal controls and subjects with Fuchs' dystrophy is unknown. If a difference were present, calculations of endothelial permeability would be affected. We have assumed that the baseline central corneal thickness for patients with Fuchs' dystrophy, before developing the disease, does not differ from the normal population. Whether this is true or not is unknown, although the central corneal thickness for the subjects with mild to moderate cornea guttata in this study did not differ statistically from the normal subjects. We also assumed that the rate of transfer of fluorescein across the endothelium is proportional to that of water and that the proportion is the same in the different groups studied. Finally, we used methods that are based on the work of Hedbys and Dohlman¹⁹ and Ytteborg and Dohlman²⁰ and the assumptions made in reaching their conclusions.

Even though endothelial permeability may be normal early in the course of the disease, it may be increased in patients with more advanced Fuchs' dystrophy with epithelial edema, since endothelial permeability cannot be measured in such corneas by this method.

Recent studies have found alterations in ouabain binding sites, adenosine triphosphatase activity, and cytochrome oxidase activity in the endothelium of patients with Fuchs' dystrophy. Geroski and associates,21 using specific binding of tritiated ouabain, reported a significant increase in Na/K adenosine triphosphatase-associated ouabain binding site density in cadaver eyes with moderate cornea guttata compared with normal cadaver eyes. Na/K adenosine triphosphatase activity was not measured in this study. Conversely, Mc-Cartney and colleagues, 22 in a more recent study using tritiated ouabain and autoradiographic techniques, found a decrease in adenosine triphosphatase-associated ouabain binding sites in the endothelium on both a per unit basis and a per cell basis in eyes with advanced Fuchs' dystrophy compared with age-matched eye bank eyes. They also noted a reduction in adenosine triphosphatase activity in the endothelium in Fuchs' dystrophy. Tuberville, Wood, and McLaughlin²³ recently described a decrease in cytochrome oxidase activity in the central corneal endothelium in Fuchs' dystrophy. Since endothelial pump function is an energyrequiring process, a decrease in pump function could be expected in cells in which oxidative phosphorylation activity is markedly decreased. The results of the present study are consistent with these recent experiments

The fluorescence polarization of the aqueous humor was statistically significantly higher in the subjects with confluent to nearly confluent guttae compared with normal subjects. This difference could be caused by the difference in corneal thickness, or possibly, a difference in the aqueous humor colloid concentration between the two groups. The actual difference was relatively small, and there was no correlation between this variable and the other variables measured in the subjects with confluent to nearly confluent cornea guttata.

Data collected for aqueous humor flow rate suggest that there could be a difference in flow between subjects with guttae and normal controls. The difference is significant using a generalized *t*-test assuming a nonlinear (quadratic) model. Two explanations for the apparent difference in variability of aqueous humor flow in these two groups are possible. The difference may be caused by a reduction in the optical uniformity of the cornea in subjects with cornea guttata. Alternatively, a real difference in rate of aqueous humor flow could be present in

at least a subgroup of patients with Fuchs' dystrophy. We cannot discern, based on these techniques, which explanation is correct. At least we know that the rate of aqueous humor flow is approximately the same in groups of persons with cornea guttata as in normals, suggesting that guttae do not result from a reduction in the rate of aqueous humor flow in most patients with Fuchs' dystrophy. An alteration in the composition of aqueous humor, however, cannot be excluded as a contributing factor.

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OPHTHALMIC MINIATURE

"There are people gifted by nature with powers of observation. Without effort they form a sharp impression of whatever is going on around them, in themselves, and in others. Also they know how to cull out of these observations whatever is most significant, typical, or colourful. When you hear such people talk you are struck by the amount that an unobservant person misses.

"Other people are unable to develop this power of observation even sufficiently to preserve their own simplest interests. How much less able, then, are they to do it for the sake of studying life itself."

Constantin Stanislavski, An Actor Prepares New York, Theatre Arts Books, 1981, p. 86

Use of Collagen Corneal Shields in the Treatment of Bacterial Keratitis

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We used an animal model of Pseudomonas keratitis to compare treatment by topical tobramycin with and without the presence of a commercially available collagen shield. Pilot studies showed a significant, 30fold increase in penetration of tobramycin into the anterior chamber in eyes with a collagen shield in place. Twenty albino rabbit eyes were inoculated with P. aeruginosa to produce stromal keratitis. After 12 hours of topical tobramycin dosing, eyes with a collagen corneal shield in place had a statistically significant (P < .01) decrease in colony forming unit counts in comparison to treated eyes without a shield and control eyes.

THE COLLAGEN CORNEAL shield was originally developed by Svyatoslav Fyodorov for use as a corneal bandage after radial keratotomy, keratorefractive procedures, and corneal abrasions. The shield is fabricated from porcine scleral tissue, which has a collagen composition closely resembling that of the human cornea. It forms a clear, pliable, thin film approximately 0.1 mm in thickness. It has a diameter of 14.5 mm and base curve of 9 mm. When the shield is hydrated by tear fluids, it softens, conforms to the corneal surface, and slowly dissolves. The first such shield approved by the Food and Drug Administration dissolves in the human eye over a period of two to 12 hours, averaging about six hours. Newer versions lasting up to 12, 24, and 72 hours have also received approval for use as a corneal bandage.

Contact lenses have been used to enhance ocular penetration of topical medications, including antibiotics. ¹⁻⁵ It has been suggested that the collagen corneal shield might act similarly as a drug delivery device, either by creating a tear reservoir and increasing the time and maintaining concentration of drug contact, or by absorbing the drug as it is dosed and then gradually redistributing it into the tear film as the shield dissolves.

Material and Methods

Penetration studies—A pilot study was performed to compare the corneal penetration in rabbits of topical tobramycin eyedrops with and without the presence of a collagen corneal shield. Rabbits were anesthetized with an intramuscular ketamine hydrochloride/xylazine mixture; no topical anesthesia was used. A collagen corneal shield was placed on six eyes of three randomly selected albino rabbits. Six eyes of three albino rabbits with no collagen shield served as controls. Topical tobramycin, 3 mg/ml, was applied to all 12 eyes at a rate of one drop per 30 minutes for a total of six doses.

Anterior chamber paracenteses were performed on all eyes 30 minutes after the last dose. All shields were noted to be intact and were removed before paracentesis. Samples of aqueous humor were analyzed for tobramycin concentrations by a standardized fluorescent polarization immunoassay.

Experimental model of Pseudomonas keratitis—An ocular isolate of Pseudomonas aeruginosa with a tobramycin minimal inhibitory concentration of 2 μ g/ml was selected. Twenty eyes of ten albino rabbits received central, intrastromal injections of 10 μ l of a suspension of 5 \times 10⁴ P. aeruginosa organisms per milliliter. Rabbits

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From the Wilmer Ophthalmological Institute (Drs. Sawusch, O'Brien, and Gottsch) and the Department of Laboratory Medicine (Dr. Dick), Johns Hopkins Hospital, Baltimore, Maryland. This study was presented in part at the Contact Lens Association of Ophthalmologists meeting, Las Vegas, Nevada, Jan. 13, 1988 and at the Association for Research in Vision and Ophthalmology meeting, Sarasota, Florida, May 1, 1988.

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were anesthetized with an intramuscular ketamine hydrochloride/xylazine mixture and topical proparacaine hydrochloride. Injections were administered under an operating microscope through a 30-gauge needle on a 100-µl syringe.

By 28 hours after inoculation, all of the infections had progressed to a moderate degree of stromal infiltration. A collagen corneal shield was placed on eight eyes of four rabbits and therapy was initiated with topical tobramycin, 3 mg/ml, one drop per 30 minutes for 12 hours. In the remaining rabbits, eight eyes of four rabbits received identical tobramycin dosing without a collagen shield and four eyes of two

rabbits received saline dosing.

The rabbits were killed 30 minutes after completion of dosing. Partial to complete dissolution of the collagen shield was noted in eyes in which a shield had been placed. All remnants of the shields were removed from the ocular surface and fornix. Uniform corneal buttons were excised using an 8.5-mm sterile trephine. Corneal buttons were washed with normal saline, processed in a tissue homogenizer, and serially diluted in normal saline. Each dilution was plated in duplicate onto trypticase soy with 5% sheep blood agar. Bacterial colony forming unit counts were then performed after overnight incubation at 37 C.

Results

Penetration studies—The mean concentration of tobramycin in aqueous humor in eyes with a collagen shield in place was $6.48 \pm 3.18 \, \mu g/ml$ (Table). The mean concentration in all eyes without a shield in place was less than $0.16 \, \mu g/ml$, the limit of detectability of the fluorescence immunoassay technique. The data show a significant (P < .01, t = 4.87), greater than 30-fold increase in tobramycin penetration into the anterior chamber in eyes with the collagen shield in place.

Experimental model of Pseudomonas keratitis— The mean \pm S.D. bacterial colony forming unit count for treated eyes with the collagen shield in place was 49.4 ± 55.4 /ml (range, 0 to 135/ml), in comparison to 313.1 ± 258.3 /ml (range, 60 to 775/ml) for treated eyes without the collagen shield in place. This difference was significant (P <.01, t=2.82), demonstrating that the collagen shield enhanced therapy. Both groups of eyes treated with tobramycin had significantly lower colony forming unit counts than the

TABLE
PENETRATION OF TOPICAL TOBRAMYCIN*

EYE NO.	COLLAGEN SHIELD	TOBRAMYCIN CONCENTRATION (μG/ML)		
Treated eyes				
1	Yes	7.33		
2	Yes	6.98		
3	Yes	7.68		
4	Yes	2.74		
5	Yes	3.00		
6	Yes	11.17		
Control eyes				
7	No	< 0.16		
8	No	< 0.16		
9	No	< 0.16		
10	No	< 0.16		
11	No	< 0.16		
12	No	< 0.16		

*Penetration of topical tobramycin (3 mg/ml) into the anterior chamber of rabbit eyes with and without a collagen shield in place. The mean \pm S.D. concentration in eyes with a collagen shield in place was 6.48 \pm 3.18 μ g/ml.

saline-treated control eyes (1.4 \times 10⁷ \pm 1.4 \times 10⁷/ml; range, 6.8 \times 10⁶ to 3.5 \times 10⁷/ml).

Discussion

The penetration data show that the collagen corneal shield acts as a drug delivery device for topical tobramycin. The shield may serve to retain drug in the tear film or absorb and gradually release drug into the tear film between doses. The collagen molecules of the shield may bind tobramycin molecules and release them upon gradual dissolution. The maintenance of drug concentration and increase in time of contact result in increased drug penetration into the cornea and anterior chamber. High initial drug levels are important in the therapy of microbial keratitis.

A potential concern is that the presence of a foreign body in the eye, such as a contact lens or collagen shield, might exacerbate keratitis by serving as a nidus for infection. The ability of *Pseudomonas* to bind to soft contact lenses has been well documented⁶⁻⁸ and correlated with contact lens-related keratitis. However, this study suggests that the collagen corneal shield may be a useful adjunct to treatment of keratitis with topical tobramycin. Since the collagen shield continuously dissolves on the ocular

surface, it may be more difficult for organisms such as *Pseudomonas* to adhere to the surface and establish a nidus of infection.

The collagen shield has been demonstrated to be useful in treatment of epithelial defects (J. Robin, unpublished data, and E. Shaw, unpublished data). The collagen shield may enhance epithelial closure of ulcers by serving as a bandage lens, although this study did not directly address this issue. By serving as a corneal bandage and as a drug delivery device, an antibiotic-soaked shield might offer superior protection against development of bacterial keratitis in patients treated for corneal abrasions.

These studies suggest that the collagen corneal shield may have a role in enhancing antibiotic therapy of microbial keratitis, either by increasing delivery of topical antibiotics, providing high initial drug levels, or by reducing the necessary dosing frequency.

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OPHTHALMIC MINIATURE

Spirit of the Hour (speaking to Prometheus):

Soon as the sound had ceased whose thunder filled

The abysses of the sky, and the wide earth,

There was a change . . . the impalpable thin air

And the all-circling sunlight were transformed

As if the sense of love dissolved in them

Had folded itself round the sphered world.

My vision then grew clear and I could see

Into the mysteries of the Universe.

Percy Bysshe Shelley, "Prometheus Unbound III," 1818–1819

The Development of Lacquer Cracks in Pathologic Myopia

Richard M. Klein, M.D., and Stuart Green, M.D.

We examined three patients with pathologic myopia who had mild visual symptoms and subretinal hemorrhages. None had subretinal neovascularization. In all three patients, lacquer crack lesions of the choroid appeared shortly after clearing of the subretinal hemorrhages. The lacquer cracks were always more extensive than the preceding hemorrhages. These findings support the theory that mechanical stretching and rupture of the Bruch's membrane-pigment epithelium-choriocapillaris complex is the cause of these lesions. Fluorescein angiography helped differentiate these subretinal hemorrhages from those caused by subretinal neovascularization.

LACQUER CRACK LESIONS are irregular, pale linear lesions of the posterior fundus found in severely myopic eyes. Their prevalence in such eyes is 4.3%. However, a much larger percentage of patients with myopic macular degeneration develop lacquer cracks. Because these lesions occur relatively early in the course of myopic macular degeneration, no histopathologic examination of lacquer cracks has been reported.2 Although the anatomic, functional, and fluorescein angiographic characteristics of these lesions have been well documented, 1,2 we found only one case in the ophthalmic literature demonstrating the natural development of lacquer crack lesions.3 We studied three cases of de novo development of lacquer crack lesions in severely myopic eyes. In all three patients, the lacquer cracks developed shortly after the appearance of subretinal hemorrhages in the absence of subretinal neovascularization.

Case Reports

Case 1

In May 1983, a 20-year-old man was examined because of subretinal neovascularization associated with myopic macular degeneration in his right eye. Visual acuity was R.E.: 20/200 and L.E.: 20/50. The asymptomatic left eye had generalized thinning of the pigment epithelium, characteristic of a myopic fundus, and there was a horizontally oriented lacquer crack below the left fovea (Fig. 1).

Three years later, in April 1986, the patient complained of sudden loss of vision, distortion, and central scotoma in the left eye. Visual acuity in that eye was 20/60. There was central distortion on Amsler grid testing. Ophthalmoscopic findings were unchanged except for the presence of a subretinal hemorrhage at the temporal edge of the fovea (Fig. 2). There was no subretinal fluid or lipid deposition. The lacquer crack appeared unchanged and behaved as a window defect on fluorescein angiography. There was no evidence of subretinal neovascularization.

Three months later, in July 1986, the patient experienced further visual loss in the left eye. Visual acuity was 20/200 and ophthalmoscopy showed a new lacquer crack extending from the original lacquer crack lesion (Fig. 3). Again, no subretinal fluid or lipid deposition was present.

Case 2

In June 1981, a 40-year-old man was examined for recent onset of blurred central vision in the left eye. Visual acuity was R.E.: 20/20 and L.E.: 20/50. Amsler grid testing showed central distortion. Ophthalmoscopy demonstrated

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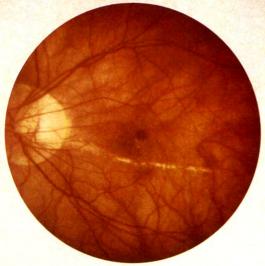


Fig. 1 (Klein and Green). Case 1, left fundus. Original appearance in May 1983. Note generalized thinning of the pigment epithelium and horizontally oriented lacquer crack below the left fovea.

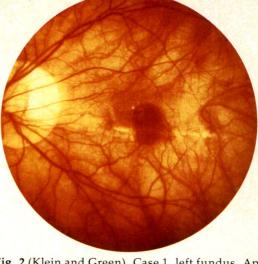


Fig. 2 (Klein and Green). Case 1, left fundus, April 1986 after the onset of a central scotoma. Note subretinal hemorrhage at the temporal margin of the fovea. Lacquer crack appears unchanged.

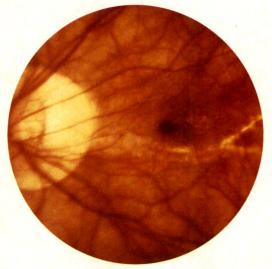


Fig. 3 (Klein and Green). Case 1, left fundus, July 1986. There is a new lacquer crack temporal to the macula and intersecting the original lesion. The subretinal hemorrhage has cleared completely.

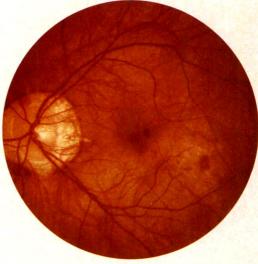


Fig. 4 (Klein and Green). Case 2, left fundus. Appearance at initial examination in June 1981. There are subretinal hemorrhages in the macula, but no lacquer cracks.

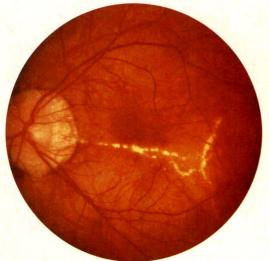


Fig. 5 (Klein and Green). Case 2, left fundus, September 1981. There is an extensive network of new lacquer cracks in the macular area. Subretinal hemorrhages have cleared almost completely.



Fig. 6 (Klein and Green). Case 2, left fundus. Appearance in November 1985. There is widening of the lacquer cracks, with pigment aggregation within the lesions.

generalized thinning of the pigment epithelium, characteristic of a myopic fundus, and there were several discrete round subretinal hemorrhages in the macula. No lacquer crack lesions were present in the macula (Fig. 4). Fluorescein angiography showed no evidence of subretinal neovascularization or other fluorescein leakage.

Three months later, in September 1981, the subretinal hemorrhages had almost completely disappeared, and there was an extensive collection of lacquer crack lesions extending across the macular area (Fig. 5). Visual acuity at this time was R.E.: 20/25 and L.E.: 20/30+3.

In November 1985, more than four years after the initial examination, the patient had no new visual complaints. Visual acuity was R.E.: 20/30-1 and L.E.: 20/40+3. Ophthalmoscopy showed widening of the lacquer cracks, with some pigment aggregation focally within the lesions (Fig. 6). Again, there was no sign of subretinal neovascularization.

Case 3

In March 1982, a 31-year-old woman was examined because of a three-day history of distortion and blurring in her left eye. Visual acuity was 20/400 in each eye. Amsler grid testing confirmed central distortion. Ophthalmoscopic examination disclosed a posterior staphyloma, with mild lacquer crack formation paracentrally, in both eyes. A round subretinal hemorrhage was present in the center of the left macula. Fluorescein angiography showed no evidence of subretinal neovascularization. One month later, the subretinal hemorrhage had disappeared and in its place was a small lacquer crack. Visual acuity had improved to 20/120 in the left eye. Subsequent examination five years later showed marked enlargement of this central lacquer crack, but no further deterioration in visual acuity.

Discussion

These cases demonstrate the formation of new lacquer crack lesions shortly after the occurrence of subretinal hemorrhages in three patients with pathologic myopia. In all three cases, the hemorrhages occurred before a lacquer crack was visible, and the typical linear, white lacquer crack lesion occurred a short time later. The lacquer crack lesions were more extensive than the subretinal hemorrhages (Cases

1 and 2), indicating that rupture of the Bruch's membrane complex was not necessarily associated with hemorrhage along its entire length.

The lacquer cracks enlarged gradually in the days and weeks following the acute break in the choriocapillaris, as the stretching forces in the wall of the staphyloma were relieved. However, as in Cases 2 and 3, there was not necessarily an associated worsening of visual acuity. The visual acuity in Patients 2 and 3 actually improved as the early lacquer cracks developed. The improvement appeared to correlate with clearing of subretinal hemorrhage.

We found no perceptible lengthening of the eye during the follow-up period of these patients on B-scan ultrasonography. This may have been the result of the limits of resolution (1.0 mm) of the B-scan ultrasound apparatus, but it is more likely because the lacquer crack lesions were simply a result of relief of latent forces in the eye wall.

Recent reports have supported the theory that lacquer cracks as well as other macular degenerative changes in pathologic myopia are caused by mechanical stretching of the retina and choroid within the posterior staphyloma.4 Our three cases provide further evidence for the mechanical theory of myopic macular degeneration because, if lacquer crack lesions were a consequence of a primary atrophic process in the choroid, hemorrhage (as seen in the present cases) would not be expected to be a common preceding event. Other investigators have also found subretinal hemorrhages in association with early changes of myopic macular degeneration unrelated to subretinal neovascularization.2,5

The clinical course in our cases emphasizes the importance of fluorescein angiography to determine whether subretinal hemorrhages in pathologic myopia are a result of rupture of Bruch's membrane complex, as in these cases, or of subretinal neovascularization. Hemorrhage associated with subretinal neovascularization sometimes requires immediate treatment by photocoagulation; hemorrhage associated with lacquer cracks alone never requires treatment.

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OPHTHALMIC MINIATURE

I let her have the argument, for I noted that Magdalena's eye was quavering, and I grew fearful. Slowly that same eyelid slid open, back to the point from which I had closed it, and the eye again fixed upon Maud and me. I leaned forward for a look but Maud tugged me back with her urgent bulldog grip. I broke her hold and looked squarely into La Última's eye by the light of the brilliant half-moon, at first seeing the conventional human orb: the maroon iris, the deep-brown pupil, the soft white transparency of the conjunctival membrane striped with the faintest of frigid purple rivers and tributaries.

William Kennedy, Quinn's Book New York, Viking Penguin Inc., 1988, p. 117

Central Sparing in Annular Macular Degeneration

John J. Weiter, M.D., Francois Delori, Ph.D., and C. Kathleen Dorey, Ph.D.

Using fluorescein angiography and monochromatic photography, we measured the size of the central sparing in 45 patients with annular maculopathy (mean \pm S.D., 0.34 \pm 0.15 disk diameter; range, 0.10 to 0.65 disk diameter) and compared it with the size of macular yellow pigment in 40 subjects (mean \pm S.D., 0.31 \pm 0.12 disk diameter; range, 0.1 to 0.5 disk diameter). The close approximation of these values suggested that macular yellow pigment contributed to the annular pattern through a photoprotective mechanism.

THE TERM BULL'S-EYE MACULOPATHY, introduced by Kearns and Hollenhorst in 1966 for cases of toxic retinopathy secondary to chloroquine usage,1 describes a peculiar annular configuration of atrophy in the perifoveal region with sparing of the fovea. It later became evident that this annular abnormality was not pathognomonic for chloroquine retinal toxicity, but also occurred in other unrelated conditions including cone dystrophy, 2,3 senile macular degeneration, Stargardt's disease, retinitis pigmentosa,4 ceroid lipofuscinosis,5,6 benign concentric annular macular dystrophy, olivopontocerebellar atrophy,8 fucosidosis,9 Hallervorden-Spatz disease, 10,11 and Sjögren-Larsson syndrome. To date, no explanation exists for the curious ringlike appearance of these different degenerations.

Previous studies of the distribution and concentration of the ocular fundus pigments (melanin, lipofuscin, and macular yellow)¹²⁻¹⁶ showed that the topographic retinal pigment epithelial lipofuscin accumulation manifests as an annular pattern in the macula. We suggested that macular yellow pigment contributed to this

appearance through a photoprotective mechanism. ¹⁷ To test this hypothesis, we studied the relationship between the size of the central sparing in patients with annular macular degeneration and the diameter of macular yellow pigment in control subjects.

Subjects and Methods

We measured the diameter of the central spared area seen on fluorescein angiograms from 45 patients showing an annular macular degeneration pattern and expressed the size in disk diameters (Fig. 1). If both eyes of patients showed a measurable annular pattern, the diameters of both eyes were averaged. The associated disease conditions included senile macular degeneration (22 cases), chloroquine retinal toxicity (seven cases), cone dystrophy (five cases), Stargardt's disease (three cases), retinitis pigmentosa (six cases), and unknown (two cases). Macular yellow pigment was demonstrated by comparing a blue-light photograph (within the absorption range of macular yellow pigment) with a green-light photograph (outside the absorption range) (Fig. 2). We then measured the diameters of the central dark spot noted on a blue-light photograph from 40 patients not showing macular disease. If studies on both eyes of the subjects were available, the measurements were averaged.

The measurements in this study were made from the routine monochromatic photographs and fluorescein angiograms used in our clinical practice. These studies were performed using Kodak Tri-X 400 ASA film, and measurements were made on the Agfa F0711P positive print transparency. The transparencies were mounted and measurements made from a projected image.

The optic disk was measured horizontally, as was the diameter of the central dark spot (used as a measure of macular yellow pigment). Many of the annular patterns of atrophy were not

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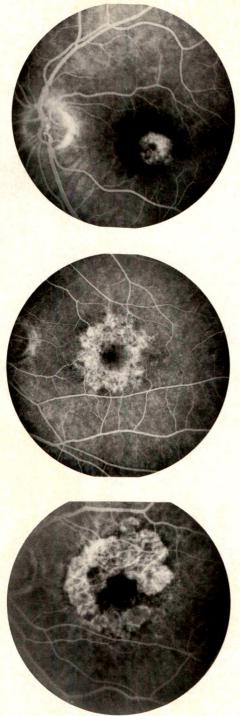


Fig. 1 (Weiter, Delori, and Dorey). Fluorescein angiograms demonstrating a spectrum of annular patterns of atrophy. Top, Cone dystrophy with a small spared central area. Middle, Cone dystrophy with a large spared central area. Bottom, Macular degeneration with an irregular and incomplete annular pattern of atrophy.

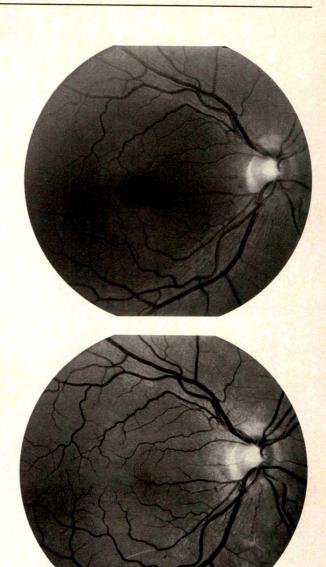


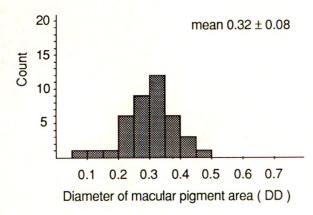
Fig. 2 (Weiter, Delori, and Dorey). Monochromatic photographs of a normal fundus. Top, Blue-light (460 to 490 nm) photograph demonstrating macular yellow in the fovea. Bottom, Green-light (530 to 550 nm) photograph. Under green-light conditions, the macular yellow is not seen. The absence of a dark spot in green light confirms that the dark spot in blue light is caused by macular yellow pigment absorption.

complete (full 360 degrees of atrophy). If complete, the measurement was made horizontally. If the annular pattern of atrophy was not complete (Fig. 1), the measurement was made of the smallest diameter within an incomplete ring of atrophy. All measurements on the projected slides were made by one of us (J.J.W.).

Results

The central area of sparing in annular macular degeneration as noted on fluorescein angiograms averaged 0.34 ± 0.15 disk diameter (mean \pm S.D.), with a range of 0.10 to 0.65 disk diameter (Fig. 3). In general, the area of central sparing in these eyes showed a greater horizontal than vertical dimension. There did not appear to be a wide difference in appearance among the various subgroups with this annular pattern of atrophy except for the patients with senile macular degeneration, in whom the annular pattern of atrophy showed marked variability, often without a complete ring of atrophy. These cases tended to have discrete lobular or geographic atrophy in a perifoveal distribution (Fig. 1).

The central dark spot representing macular yellow on monochromatic photographs mea-



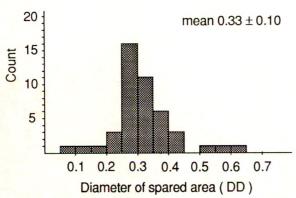


Fig. 3 (Weiter, Delori, and Dorey). Top, Histogram showing distribution of size of macular yellow. Bottom, Histogram showing distribution of size of central spared area in annular patterns of atrophy. DD, disk diameter.

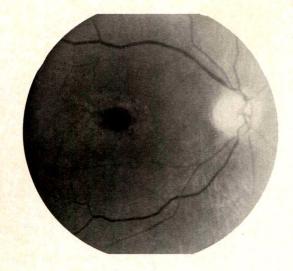
sured 0.31 ± 0.12 disk diameter, with a range of 0.1 to 0.5 disk diameter (Fig. 3), and showed a normal distribution. Its limits were not well defined, rendering these measurements relatively subjective. The horizontal dimension of the central dark spot tended to be greater than the vertical. (Caution should be exercised, however, since this may have been an optical artifact related to the foveal reflections.) These measurements compared closely with previous ones made in our laboratory with narrow-band spectral illumination centered on 470 nm and high-contrast film. 15 Under these conditions, the diameter of the central dark spot in 40 normal subjects averaged 0.26 disk diameter, with a range of 0.1 to 0.4 disk diameter. The nonparametric Mann-Whitney test was used to compare the median diameter of macular yellow in the normal sample with the median diameter of central sparing in the sample with the annular atrophic lesions, because of outliers in the latter group. No significant difference was found between the groups.

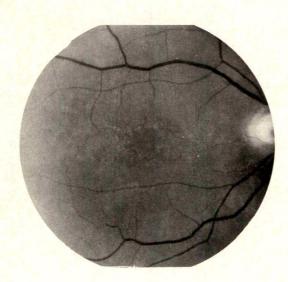
In several cases, good monochromatic fundus photographic studies were performed on individuals showing the annular macular degeneration pattern. The area of the central dark spot representing macular yellow corresponded identically with the area of central sparing seen in the annular degeneration pattern (Fig. 4).

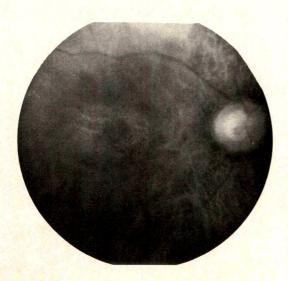
Discussion

The entities associated with atrophic annular macular lesions can be divided into two major groupings that seem to be related either to the use of photosensitizing drugs (type I), such as chloroquine, ¹⁸⁻²⁰ or to disease states characterized by a buildup of lipofuscin-like material in the retinal pigment epithelium (type II), such as ceroid lipofuscinosis, ⁵ cone dystrophy, ²¹ fundus flavimaculatus, ²² retinitis pigmentosa, ^{23,24} Sjögren-Larsson syndrome, ²⁵ and senile macular degeneration. ¹³

We propose that both types of annular maculopathies derive from oxidative damage to the photoreceptor-retinal pigment epithelial complex that is attenuated over the fovea by the presence of macular yellow. Type I damage results from melanin-binding photosensitizers, ¹³ with the greatest damage at the posterior pole because of the increased retinal pigment epithelial melanin ¹⁴ with central sparing







caused by the photoprotective effect of macular yellow. 26 Type II damage is related to oxidation of the photoreceptor-retinal pigment epithelial complex, resulting in an accumulation of lipofuscin material. Lipofuscin in the retinal pigment epithelium has been shown to accumulate in the normal eye, with peak accumulation at the posterior pole and a depression (reduction) in the region of the fovea. 12,14 If excessive lipofuscin concentration is detrimental to the retinal pigment epithelial cells, 14,27 then the degenerative fundus pattern associated with excessive lipofuscin accumulation would have an annular pattern (Fig. 5).

There are three possible hypotheses as to how this theory may explain the small area of central sparing in annular macular degeneration. First, an inverse relationship exists between melanin and lipofuscin concentration in the retinal pigment epithelium. 14 Thus, as retinal pigment epithelial melanin peaks at the fovea, there is an associated reduction in retinal pigment epithelial lipofuscin. A second possibility is the protective effect from the presence of macular yellow pigment in the fovea, which serves to reduce the amount of blue light striking this area.28 Since lipofuscin is thought to be related to oxidative mechanisms, 29,30 the absorbance of short-wave visible radiation^{31,32} by macular yellow pigment should help protect against damage that causes retinal pigment epithelial lipofuscin accumulation. Third, macular yellow pigment, like other carotenoids, may also have a direct antioxidant effect and thereby reduce the oxidative consequences of light of any wavelength.

As evidence that macular yellow plays a role, we measured the area of macular yellow in normal eyes and found that it corresponded to the size of the central spared area of annular macular degenerations. The cases in which macular yellow and an annular pattern of atrophy could be measured in the same eye were

Fig. 4 (Weiter, Delori, and Dorey). Monochromatic photographs of an eye with an annular pattern of atrophy secondary to chloroquine retinal toxicity. Top, Blue-light (460 to 490 nm) photograph; middle, green-light (530 to 550 nm) photograph; bottom, red-light (630 to 650 nm) photograph. Note that the area of macular yellow pigment seen under blue light coincides with the area of central sparing noted in the red-light photograph.

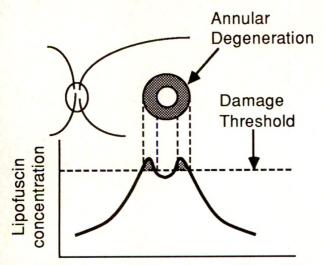


Fig. 5 (Weiter, Delori, and Dorey). Model relating lipofuscin concentration in the retinal pigment epithelium to the development of an annular atrophic lesion. We hypothesize that photoabsorption by macular yellow pigment contributes to a decrease in lipofuscin concentration corresponding to the region of central sparing typical of the annular pattern of atrophy.

particularly interesting, because the areas of macular yellow and central sparing overlapped remarkably well (Fig. 4). We believe the close approximation of these measurements suggests that macular yellow pigment contributes to the annular pattern through a photo-oxidation protective mechanism.¹⁷

The presence of macular yellow pigment was recognized over 200 years ago.33 The yellow color is caused by a carotenoid that can be found throughout the retina, but has its highest concentration in the foveal region. 16,28 Wald34 identified this yellow pigment as lutein, a carotenoid originating in the green leaves of plants. The macular pigment has a maximum absorbance in the blue wavelengths (460 nm) and is most dense in the photoreceptor axon and inner plexiform layers, with density declining markedly with retinal eccentricity.28 All carotenoids, including macular yellow pigment, in humans are derived from the diet. Monkeys fed a xanthophyll-free diet from birth have no detectable macular yellow pigment, in contrast to monkeys fed a standard diet including carotenoids. 35

The most widely accepted role of macular yellow pigment is that of reducing chromatic aberration and therefore improving visual acuity. 36 Protecting the retina from light damage

may be another important role, since the pigment absorbs wavelengths known to be especially damaging to the retina. This is consistent with studies of chronic light damage in monkeys showing that the area of greatest damage is perimacular, with sparing of about 2 degrees in the central macula (or about 0.34 disk diameter).

Macular yellow pigment may also have a protective effect on the retinal phototoxicity associated with the operating microscope. 38,39 In humans, these photic lesions in the retina appear to be eccentrically located in relation to the fovea, which has been attributed to a protective role by macular yellow.38 In a human experiment,38 the patient subjectively gazed directly at the center of the light, but the retinal lesion was eccentrically located, and central visual acuity was affected only minimally. In a similar experiment in a monkey,39 there was attenuation of the retinal phototoxic lesion in the foveal region. These findings support the observation that the threshold for production of retinal lesions by blue monochromatic light is nearly twice as great inside as outside the fovea.31

Macular yellow pigment may also have a direct antioxidant effect. In humans, there do not appear to be biologic variations in the macular yellow pigment density. Studies of West Indian and European populations correlating the density of macular yellow pigment with ethnic group, environment, age, and color of skin, hair, and eyes showed no difference except for a higher density in red-haired individuals. In the difference in the state of the st

Our measurements of the distribution of macular yellow pigment in the human retina are similar to those inferred from human psychophysical methods using color matching,42 flicker sensitivity, 43 and two-color increment thresholds⁴⁴ and consistent with anatomic measurements in the monkey retina. 16 These measurements show that macular yellow pigment is greatest at the center of the fovea and drops to a low, fairly consistent level within an area whose diameter is 1 mm or 4 degrees. Since there is macular yellow pigment throughout the retina, with the highest density at the fovea, the results from different methods of measurement will vary somewhat. Indeed, our present measurements varied slightly from our previous studies that used narrow-band spectral illumination and high-contrast film, resulting in a better-defined edge. In the present study, we used our routine clinical fluorescein angiography technique, thereby allowing use of our routine patient records, which resulted in a less well-defined edge for the measurement of macular yellow.

Finally, this proposed mechanism for annular macular lesions also may relate to canthaxanthin retinopathy, which results from ingestion of the photosensitizer canthaxanthin. 45 The resultant retinopathy demonstrates an annular pattern of crystals in the neurosensory retina. 45-47 However, the primary effect of the photosensitizer appears to be on the photoreceptors and retinal pigment epithelium. 48

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OPHTHALMIC MINIATURE

And I have known the eyes already, known them all—
The eyes that fix you in a formulated phrase,
And when I am formulated, sprawling on a pin,
When I am pinned and wriggling on the wall,
Then how should I begin
To spit out all the butt-ends of my days and ways?
And how should I presume?

T. S. Eliot, "The Love Song of J. Alfred Prufrock," 1915

Effect of Intravitreal Liquid Silicone on Optic Nerve Function

U. Kellner, M.D., K. Lucke, M.D., and M. H. Foerster, M.D.

We recorded visual-evoked cortical potentials before and after pars plana vitrectomy and intravitreal liquid silicone filling in 30 patients (30 eyes) with complicated retinal detachments without vascular eye disease or glaucoma. The flash- and flicker-evoked cortical potentials increased in amplitude in all cases. Of 21 eyes followed up for more than 50 days, eight had a 30-Hz flicker response before and after surgery. Of 13 eyes with preoperatively reduced flicker-frequency responses, ten (77%) were improved after surgery. The visual-evoked cortical potential parameters did not deteriorate in any of the patients. We concluded that no toxic effect of intravitreal liquid silicone on the optic nerve could be shown by electrophysiologic methods.

THE TECHNIQUE OF liquid silicone filling as it is used to treat complicated retinal detachments has evolved over the last quarter century. 1-6 Today, vitrectomy and intravitreal silicone filling combined are used only when other therapeutic approaches are unlikely to be successful.3-7 Silicone-related complications include cataract, keratopathy, and secondary glaucoma.2,8 Some patients develop optic nerve atrophy after intravitreal liquid silicone filling.6 Possible reasons include continuously increased intraocular pressure as a result of secondary neovascular glaucoma, angle closure, silicone emulsification, ischemic optic nerve disease, particularly in diabetic patients, and a toxic effect of liquid silicone. We, therefore, investigated the optic nerve function using visual-evoked cortical potentials before and after pars plana vitrectomy and intravitreal liquid silicone injection.

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Patients and Methods

Thirty-eight consecutive patients (38 eyes) with complicated retinal detachments including the macula without vascular eye disease or glaucoma were included in this study. They underwent pars plana vitrectomy and intravitreal silicone filling with purified silicone (viscosity, 5,000 centistokes). Before silicone surgery, intraocular pressure in all patients was normal. Eight patients were excluded from the study because of postoperative retinal redetachment or persisting secondary glaucoma. Five (17%) of the remaining patients had shortterm postoperative increases in intraocular pressure that were treated successfully with 0.5% timolol and 0.1% dipivefrin eyedrops twice a day; they all remained in the study. The indications for silicone filling in the 30 patients remaining in the study were proliferative vitreoretinopathy in 20 cases, giant tears in six cases, and posterior retinal holes in four cases.

The electrophysiologic examinations included the recording of flash- and flicker-evoked cortical potentials before and after silicone surgery. Twenty-one patients were followed up for more than 50 days (mean \pm S.D., 179 \pm 103 days), and 13 of these patients were followed up for more than 150 days (238 \pm 64 days).

The examinations were performed with dilated pupils. The electrodes were placed in standard positions at the vertex and 2 cm above the inion. The ear served as the reference ground. A 100-diopter contact lens provided uniform retinal illumination. The light stimuli were of 10-msec duration, with a light intensity of 780 cd/m² in eyes with retinal detachment. Light stimuli were reduced by one logarithmic unit in eyes with attached retinas. First single flash stimuli were used, followed by flicker stimuli with the frequencies of 5, 10, 20, and 30 Hz (Fig. 1). Sixty-four responses were averaged with every stimulus.

We measured the amplitude of the flashevoked cortical potential and the implicit time

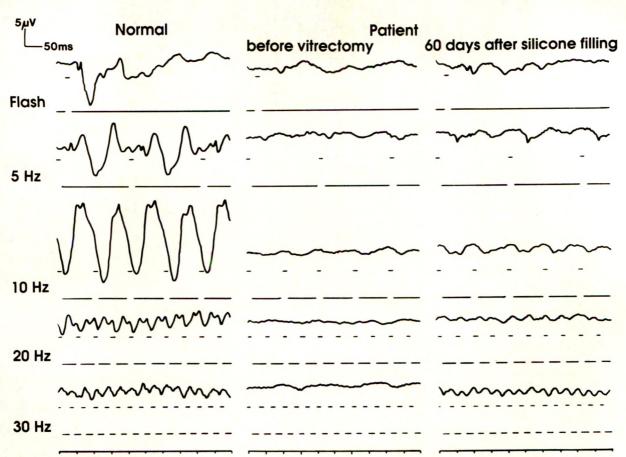


Fig. 1 (Kellner, Lucke, and Foerster). Flash- and flicker-evoked cortical potentials, stimulus duration 10 msec. Lower trace indicates the light stimuli. Upper trace is the average of 64 sweeps; positivity is recorded downward. Left column, Normal flash- and flicker-evoked cortical potential. Middle and right columns, Flash- and flicker-evoked cortical potentials before and after silicone filling because of proliferative vitreoretinopathy. Before surgery, the flicker responses were detectable up to 10 Hz with minimal amplitude; 60 days after surgery, the flicker-evoked cortical potential could be detected up to 30 Hz with increased amplitudes.

of the highest positive component, the P2-component. The amplitudes of the flicker-evoked cortical potentials were determined, and we estimated the highest frequency response. All normal fellow eyes responded to stimulus frequencies of up to 30 Hz (Table) or more. The high interindividual variance of the amplitudes of the flicker-evoked cortical potentials resulted in a wide normal range. Stimulus frequencies above 30 Hz were not analyzed because no significant data could be obtained at higher frequencies.

Of our 30 patients, 27 had a normal fellow eye. The visual-evoked cortical potentials of these eyes showed normal flicker responses at all frequencies tested.

TABLE

NORMAL AMPLITUDES OF FLICKER-EVOKED

CORTICAL POTENTIALS

STIMULUS FREQUENCY* (Hz)	$\begin{array}{c} \text{MEAN} \pm 2 \text{ S.C} \\ \text{AMPLITUDE} \\ (\mu\text{V}) \end{array}$		
Flash	22 ± 16		
5	17 ± 8		
10	17 ± 10		
20	8 ± 5		
30	6 ± 4.5		
40	3.2 ± 3		
50	1.5 ± 2		

^{*}Stimulus frequencies above 30 Hz gave no statistically significant data.

Results

Preoperatively, because of retinal detachment, all eyes had reduced amplitudes of the visual-evoked cortical potentials compared with the normal fellow eyes at all stimulus conditions. However, the reduced amplitudes were still within the low-normal range. Early and late flash-evoked cortical potential subcomponents representing rhythmic response characteristics had markedly reduced amplitudes. The implicit time of the P2-component was not different in eyes with retinal detachment compared to the normal fellow eyes. Flicker-evoked cortical potentials were found up to stimulus frequencies of 10 Hz in seven eyes, up to 20 Hz in 11 eyes, and up to 30 Hz in 12 eyes.

The postoperative amplitudes of the visualevoked cortical potentials, after the retina was reattached, were increased from their preoperative values. The single flash-evoked cortical potential had more subcomponents than before vitrectomy. The implicit time of the P2component did not change significantly. Figure 1 shows the flicker-evoked cortical potentials of a normal subject (left) and a typical patient before (middle) and 60 days after surgery (right).

The maximal frequency response did not decrease after surgery in any of the 30 study eyes. The results of the flicker-evoked cortical potentials in 21 eyes with a follow-up of more than 50 days are shown in Figure 2. Eight eyes had a 30-Hz flicker response preoperatively (the

highest flicker frequency tested) and had the same response at every follow-up examination. Ten of the remaining 13 eyes (77%) had an increased frequency response after silicone filling. In six of these ten eyes, this occurred immediately after surgery. No change occurred after surgery in three eyes with preoperatively reduced frequency responses.

Of the 13 eyes that were followed up for more than 150 days, five had a 30-Hz flicker stimulus response before surgery and at the last follow-up examination. Seven of the remaining eight eyes had flicker responses at higher frequencies at their last follow-up examination compared to preoperatively (Fig. 3).

One eye each underwent silicone removal after 158, 194, and 257 days. The amplitudes of the visual-evoked cortical potential did not change after compared to immediately before silicone removal. The frequency response was unchanged as well: two eyes had 30-Hz flicker responses and one eye 20-Hz flicker responses before and after silicone removal.

Ophthalmoscopically, we found no increasing excavation or paleness of the optic nerve head in any of the eyes during the study.

Discussion

Histologic and electrophysiologic findings in human and animal eyes having undergone silicone surgery have been contradictory and different conclusions regarding liquid silicone toxicity have been made. 9-15 In enucleated eyes after silicone surgery, vacuole formation has

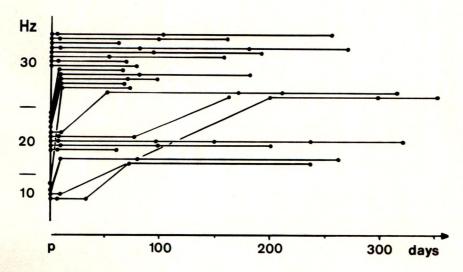


Fig. 2 (Kellner, Lucke, and Foerster). Flicker-evoked cortical potentials. Frequency responses at the preoperative (p) and postoperative follow-up examinations. Dots indicate the highest frequency response at a given examination. Each line represents one eye (n = 21).

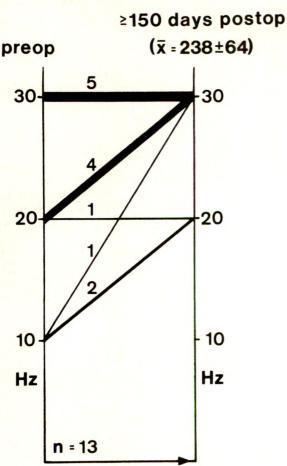


Fig. 3 (Kellner, Lucke, and Foerster). Flickerevoked cortical potential. Highest frequency response preoperatively and at the last examination in eyes followed up for more than 150 days. Horizontal lines indicate unchanged frequency responses, oblique lines indicate changes.

been seen in the retina, the optic nerve, and even beyond the lamina cribrosa. 11,16 In animal experiments, vacuole formation and destruction of ganglion cells following silicone injection have been described. 9,17

Pattern-evoked cortical potentials would be the most accurate method to determine optic nerve function. However, good visual acuity is necessary for this test. Because of the retinal detachments in our patients, visual acuity was insufficient to record pattern-evoked cortical potentials. However, a flash-evoked cortical potential alone does not provide reliable information about optic nerve function. ¹⁸ We therefore used flicker-evoked cortical potentials as an indicator of the transmission properties of the optic nerve. ^{19,20}

In our patients there was no deterioration of the transmission properties of the optic nerve during the silicone filling and after silicone removal within an observation period of up to 348 days. In most cases, optic nerve transmission was improved. Flicker responses were unaltered or appeared at higher stimulus frequencies over time.

We believe that the optic atrophy found in some patients undergoing silicone surgery can usually be attributed to increased intraocular pressure or vascular ischemic damage. There is no clinical or histologic^{12,15,21-23} evidence to support the contention of a toxic effect of liquid silicone on the optic nerve. The swelling of the nerve fiber layer and the vacuolization and degeneration of ganglion cells described by some investigators^{9,17,24} could not be reproduced by others and were judged as "results of procedures other than silicone injection."¹²

The histologic finding of silicone vacuoles in the optic nerve head of enucleated human eyes^{11,16} was probably the result of long-standing severe disease, with retinal detachment and secondary glaucoma.¹⁴ Therefore, these results cannot be compared with those of eyes operated on successfully.

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OPHTHALMIC MINIATURE

The marriage of the wall-eyed Catrina to Jacobus, who remained cross-eyed into adulthood, was a matter of considerable discussion in Albany, and it was speculated they would give birth to children who could look both left and right at the same time they were looking straight ahead. Social conversation with Catrina and Jacobus together was also said to be a nerve-racking experience since one never knew to which of the four eyes one should properly send one's gaze.

William Kennedy, Quinn's Book New York, Viking Penguin Inc., 1988, p. 24

Transient Severe Visual Loss After Panretinal Photocoagulation

Robert C. Kleiner, M.D., Michael J. Elman, M.D., Robert P. Murphy, M.D., and Fredrick L. Ferris III, M.D.

Seven diabetic patients experienced severe but transient visual loss after panretinal photocoagulation for proliferative diabetic retinopathy. In all patients, visual acuity decreased shortly after treatment to levels ranging from 5/200 to no light perception. In five of the patients, no observable ocular disease or surgical complications could explain the degree of visual loss. The other two patients developed exudative macular detachments, although it was not clear that this change accounted for their severe visual loss. Vision improved in all patients over a period ranging from nine days to nine months. In five patients, visual acuity returned to within two Snellen lines of the pretreatment level.

PANRETINAL PHOTOCOAGULATION decreases the risk of severe visual loss from proliferative diabetic retinopathy.¹ Although relatively safe, visual loss can occur immediately after panretinal photocoagulation because of exudative retinal detachment, macular edema, choroidal detachment, secondary glaucoma, or complications of retrobulbar anesthesia.²⁴ We examined seven patients who experienced profound but temporary visual loss after panretinal photocoagulation for proliferative diabetic retinopathy. In five of these patients, the degree of visual loss could not be explained by any observable ocular disease or complications of the procedure.

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From the Wilmer Ophthalmological Institute, the Johns Hopkins Hospital, Baltimore, Maryland. Dr. Kleiner was a 1985–1986 Heed Foundation Fellow.

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Case Reports

Case 1

A 22-year-old man had insulin-dependent diabetes for 18 years. His disease had been complicated by diabetic nephropathy, hypertension, increased serum cholesterol levels, angina, and cerebrovascular accidents. In December 1980, he developed bilateral optic neuropathy, which resulted in a visual acuity of 20/60 and temporal optic nerve pallor in both eyes.

On March 1, 1985, visual acuity was 20/100 bilaterally. Both fundi showed marked ischemic changes, with numerous nerve fiber layer infarcts and intraretinal microvascular abnormalities (Fig. 1). There was florid disk neovascularization, with multiple areas of neovascularization elsewhere, in both eyes. Moderate macular edema was present bilaterally. Because the patient met the high-risk criteria of the Diabetic Retinopathy Study,⁵ panretinal photocoagulation (900 spots, argon blue-green, 500 µm) was applied to his left eye following a retrobulbar injection of 3 ml of 2% lidocaine. There were no complications associated with either the anesthetic injection or the laser treatment.

Three days later, visual acuity decreased to hand motions at 2 feet in the left eye. Slit-lamp examination showed a deep anterior chamber in the left eye. Intraocular pressure was 20 mm Hg. Shallow choroidal detachments were noted in the periphery of the left fundus. There was also a moderate exudative detachment inferiorly in the macula (Fig. 2). There was no evidence of impaired blood flow in the central retinal artery or its major branches. The same day, the patient received an additional 700 spots of argon laser panretinal photocoagulation after administration of retrobulbar anesthesia.

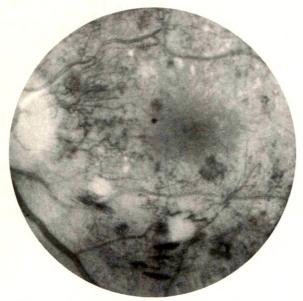
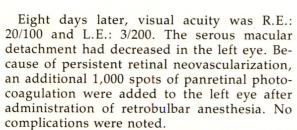


Fig. 1 (Kleiner and associates). Patient 1, left eye, pretreatment. Marked ischemia with nerve fiber layer infarcts, intraretinal microvascular abnormalities, disk neovascularization, capillary nonperfusion, and macular edema.



Two days later, visual acuity was R.E.: 20/100 and L.E.: no light perception. Externally, the left eye was not injected. Slit-lamp examination again showed a deep anterior chamber. Intraocular pressure by applanation tonometry was R.E.: 18 mm Hg and L.E.: 12 mm Hg. In the left fundus, the peripheral choroidal detachments had flattened and the serous macular detachment continued to decrease (Fig. 3). The major retinal arterioles remained patent, no vitreous hemorrhage was noted, and no laser scars were present in the macula.

On fluorescein angiography (Fig. 4), fluorescein dye first appeared in the retinal vessels and choroid at 13.7 seconds. There was normal fluorescence of the optic nerve. Large confluent areas of capillary nonperfusion were noted in the periphery. In the macula, there was moderate capillary nonperfusion and late leakage. On electroretinography, the photopic response

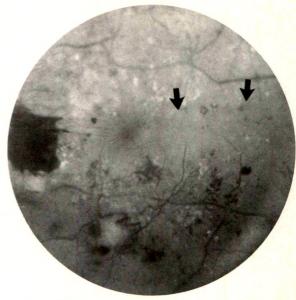


Fig. 2 (Kleiner and associates). Patient 1, left eye, three days posttreatment. Exudative detachment (arrows) is present in the macula. New preretinal hemorrhage near optic nerve does not cover the fovea.

was 73 μ V in the right eye and 0.0 μ V in the left eye (normal, >100 μ V). The scotopic response was 300 μ V in the right eye and 50 μ V in the left eye (normal, >300 μ V).

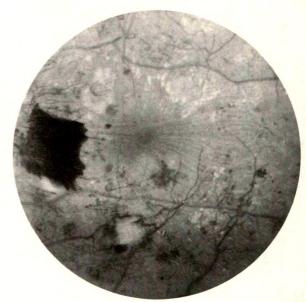


Fig. 3 (Kleiner and associates). Patient 1, left eye, 11 days posttreatment. Exudative macular detachment has flattened.

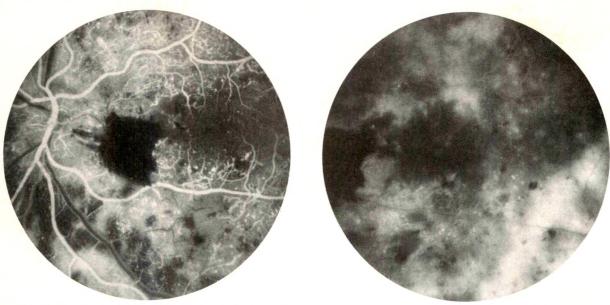


Fig. 4 (Kleiner and associates). Patient 1, left eye, 11 days posttreatment. Left, Midtransit and right, late phase fluorescein angiograms. Numerous areas of nonperfusion with late leakage in macula.

The patient subsequently received 2,000 spots of panretinal photocoagulation in his right eye, administered in four treatment sessions over three months. These were not accompanied by retrobulbar injection, and the patient experienced no visual loss in his right eye.

In May 1985, visual acuity was R.E.: 20/80 and L.E.: 20/120. Ophthalmoscopy showed some decrease in the neovascularization, with no change in the moderate macular edema in either eye (Fig. 5). Over the next several months, the neovascularization and macular edema progressed rapidly in both eyes and the patient suffered a vitreous hemorrhage in his right eye. However, a visual acuity of 20/160 was retained in his left eye. In September 1985, the patient died of a myocardial infarction.

Case 2

A 23-year-old man with insulin-dependent diabetes for 14 years had been followed up for severe preproliferative diabetic retinopathy in both eyes. In September 1982, he began using an insulin pump. In October 1983, visual acuity was 20/16 in each eye, but both fundi appeared markedly ischemic with venous tortuosity, numerous nerve fiber layer infarcts, and large areas of capillary nonperfusion. The right fundus had neovascularization on the superior temporal arcade, and the left fundus had neo-

vascularization of the disk and along the super-otemporal and inferonasal arcades. Panretinal photocoagulation (1,000 spots, argon bluegreen, 500 μm) was applied to the left eye after a retrobulbar injection of 4 ml of 2% lidocaine with epinephrine. No complications were noted.

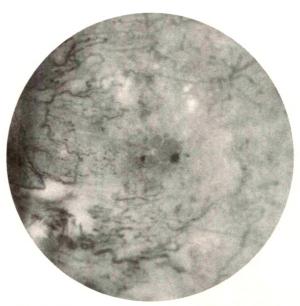


Fig. 5 (Kleiner and associates). Patient 1, left eye following visual recovery. Macular edema persists.

On postoperative day 1, the patient noted that he could barely see his hand moving in front of his face using his left eye. He returned for a repeat examination six days later, at which time visual acuity in the left eye had improved to 20/25. Goldmann perimetry, however, showed marked constriction of the left visual field (Fig. 6, left). Slit-lamp examination showed deep anterior chambers. Examination of the left fundus showed inferior intraretinal edema not involving the macula and early regression of the neovascularization. One month later, the patient stated that the vision in his left eye had returned to normal. Visual acuity remained at 20/25 in the left eye, with minimal macular edema. The patient received an additional 500 spots of panretinal photocoagulation after administration of topical anesthesia for residual disk neovascularization. This did not result in any further visual loss. Two months later, he underwent panretinal photocoagulation (1,600 spots over four sessions after administration of topical anesthesia) in his right eye for increasing neovascularization. Again, this did not result in any visual loss.

On the last follow-up examination in May 1986, visual acuity remained 20/25 in the left eye. Repeat visual field testing showed only slight constriction of the peripheral isopters, with several small scotomas in the periphery (Fig. 6, right).

Case 3

A 38-year-old woman with insulindependent diabetes for 30 years had received 1,600 spots of panretinal photocoagulation in her right eye without complication. On Nov. 18, 1982, visual acuity was R.E.: 20/125 and L.E.: 20/50. Ophthalmoscopy of the left eye showed marked neovascularization of the disk, with moderate macular edema. The patient received panretinal photocoagulation (1,401 spots, argon blue-green, 500 µm) in the left eye, without retrobulbar injection.

Two days after treatment, visual acuity was light perception in the left eye. Although the anterior chamber of the left eye was shallow, the intraocular pressure was 19 mm Hg. Ophthalmoscopy of the left eye showed mild macular edema and a shallow serous detachment of the macula. Shallow, peripheral choroidal detachments were present for 360 degrees.

On Dec. 1, 1982, visual acuity had improved to 20/200 in the left eye. The macular edema and choroidal detachments in the left eye were noted to be decreased. In July 1983, visual acuity in the left eye had recovered to 20/80. At that time, the patient received focal laser photocoagulation to the macula for persistent macular edema. On follow-up examination in April 1984, visual acuity in the left eye was 20/50.

Case 4

A 61-year-old man was first examined in October 1980. He had a 14-year history of diabetes, but had been insulin dependent for only the previous two years. Visual acuity was R.E.: 20/100 and L.E.: 20/75. Both fundi were markedly ischemic with venous dilation, numerous nerve fiber layer infarcts, intraretinal microvascular abnormalities, and moderate

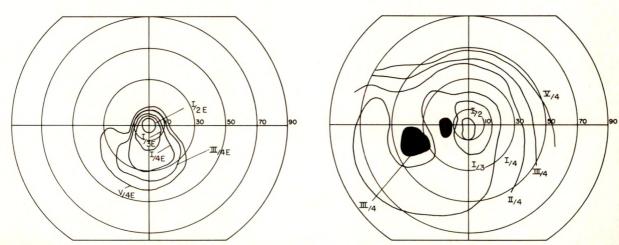


Fig. 6 (Kleiner and associates). Patient 4, visual field left eye. Left, one week posttreatment. Right, 30 months posttreatment. Visual field is nearly full with small peripheral scotomas.

macular edema. The patient received panretinal photocoagulation in the nasal retina of the right eye (574 spots, argon blue-green, 500 μ m). No retrobulbar injection was given.

One week later, visual acuity was R.E.: 5/200 and L.E.: 20/100. The appearance of the right fundus was unchanged. Fluorescein angiography showed no change in the macular leakage compared to the pretreatment study. Three weeks later, visual acuity had improved to 20/100 in the right eye. The patient's panretinal photocoagulation was subsequently completed and he had no further loss of vision.

Case 5

28-year-old woman with insulindependent diabetes for 16 years had received a total of 2,780 spots of panretinal photocoagulation in her left eye for disk neovascularization associated with vitreous hemorrhage. In March 1985, visual acuity was R.E.: 20/20 and L.E.: 20/60. Results of external and slit-lamp examinations were normal. Ophthalmoscopy of the right eye showed some lipid accumulation temporal to the macula, but no evidence of neovascularization or vitreous hemorrhage. In the left eye, inferior vitreous hemorrhage, persistent neovascularization of the disk, and an incomplete posterior vitreous detachment were noted. A large foveal cyst was centered in an edematous macula. Fluorescein angiography showed marked capillary nonperfusion of the macula, with diffuse late leakage. After a retrobulbar injection of 3 ml of 2% lidocaine without epinephrine, the patient received focal laser treatment in the left macula (250 spots, 50 to 100 µm) as well as additional panretinal photocoagulation (1,325 spots, argon blue-green, 500 μm). No complications were noted.

The patient returned for examination three weeks later. Visual acuity was R.E.: 20/20 and L.E.: 2/200. An afferent pupillary defect was now present in the left eye. Slit-lamp examination showed well-formed anterior chambers. Intraocular pressures were R.E.: 21 mm Hg and L.E.: 19 mm Hg. The edema of the left macula was unchanged. The central retinal artery and its major branches were well perfused and the vitreous hemorrhage had not increased. Fluorescein angiography showed no delayed filling of the retinal vessels. The optic nerve fluoresced normally. Laser scars were not seen within the foveal avascular zone. Fluorescein leakage into the macula appeared decreased compared to the pretreatment photographs. On electroretinography, the photopic response

was 150 μ V in the right eye and 0.0 μ V in the left eye (normal, >100 μ V). The scotopic response was 703 μ V in the right eye and 0.0 μ V in the left eye (normal, >300 μ V).

Two weeks later, visual acuity was L.E.: 4/200. When examined in July 1985, visual acuity had improved to 20/160 in the left eye, and she continued to show an afferent pupillary defect in that eye. The neovascularization in the left eye had regressed and the vitreous hemorrhage had cleared. There was no macular edema. By September 1985, visual acuity in the left eye had improved to 20/100, and by December 1985, it had returned to its pretreatment level of 20/60.

Case 6

31-year-old woman with insulindependent diabetes for 20 years was first examined on Oct. 7, 1982. Visual acuity was R.E.: 20/80 and L.E.: 20/16. Results of external and slit-lamp examinations were normal. Examination of the right fundus showed florid disk neovascularization, with numerous large fronds of neovascularization elsewhere and extensive fibrovascular tissue along the superior and temporal arcades. There was no apparent tractional detachment. The retina was markedly ischemic, and mild edema was present in the macula. Several subhyaloid hemorrhages were observed posteriorly, and mild vitreous hemorrhage was present. The left retina appeared markedly ischemic and the macula was mildly edematous. Several small fronds of neovascularization elsewhere were noted along the temporal arcades. Panretinal photocoagulation was performed in the right eye (1,230 spots, argon blue-green, 500 µm) after administration of retrobulbar anesthesia. No complications were noted.

Three weeks later, visual acuity was R.E.: 3/200 and L.E.: 20/16. An additional 402 spots of laser photocoagulation were applied to the right eye after administration of topical anesthesia. Two weeks later, visual acuity was R.E.: 8/200, and the neovascularization was regressing. The macula was not detached and the subhyaloid hemorrhages had cleared somewhat. No significant macular edema was present. The patient refused further panretinal photocoagulation to either eye. Two months after the initial treatment, visual acuity in her right eye had improved to 20/160. The patient subsequently suffered severe visual loss in both eyes secondary to fibrovascular proliferation and vitreous hemorrhage.

Case 7

57-year-old woman with dependent diabetes for 25 years had received panretinal photocoagulation for proliferative diabetic retinopathy in both eyes. On Dec. 3, 1985, visual acuity was R.E.: 20/300 and L.E.: 12/200. Examination of the right fundus showed a small amount of dispersed vitreous hemorrhage with considerable neovascularization along the superior and inferior temporal arcades. The left eye showed denser vitreous hemorrhage, with several areas of neovascularization and traction inferior to the macula. In both eyes, the retina was severely ischemic, with marked venous tortuosity and intraretinal hemorrhages. Both maculas were markedly edematous with cystic changes.

The patient received panretinal photocoagulation in the left eye (900 spots, argon bluegreen, $500~\mu m$) followed one week later by panretinal photocoagulation in the right eye (976 spots). There were no complications associated with either session. Retrobulbar injection was not given for either treatment.

When the patient returned one month later, she related gradual loss of vision in her right eye following her laser treatment. On examination, visual acuity was R.E.: hand motions at 1 foot and L.E.: 20/300. Confrontation visual fields of the right eye were markedly constricted. An afferent pupillary defect was noted in the right eye. Slit-lamp examination showed well-formed anterior chambers. Intraocular pressure by applanation tonometry was R.E.: 20 mm Hg and L.E.: 16 mm Hg. Examination of the right fundus showed normal perfusion of the central retinal artery. Persistent vitreous hemorrhage noted inferiorly did not obscure the macula. The macular edema was increased slightly, barely exceeding the degree of edema in the left eye. Fluorescein angiography showed no delay in filling of the retinal vessels and normal fluorescence of the optic nerve. In the macula, marked capillary nonperfusion and diffuse late leakage were observed. A Wintrobe erythrocyte sedimentation rate was 63 mm/hour. Results of computed tomography of the head and orbits, including the optic nerve and chiasm, were normal.

Two weeks later, visual acuity remained at hand motions in the right eye. By February 18, 1986, however, it had improved to 1/200 in the right eye. On last examination April 23, 1986, there was no change in visual acuity. The afferent pupillary defect in the right eye persisted and the macular edema remained unchanged.

Results

All of our patients were insulin dependent. In five of the patients, the onset of diabetes was before age 20 years. Pretreatment visual acuities ranged from 20/16 to 20/300 and decreased to levels ranging from 5/200 to no light perception (Table 1). Five of the patients experienced return of visual acuity to within two Snellen lines of the pretreatment level. The treatment characteristics are summarized in Table 2.

Some degree of visual recovery occurred in four months or less in all patients, but the time of onset and duration of visual loss in the seven patients was somewhat variable. Patients 1, 2, and 3 all lost vision in three days or less. Patients 2 and 3 both regained vision in less than two weeks. Likewise, Patients 4, 5, 6, and 7 lost vision over one to four weeks and regained vision over a period of three weeks to four months.

Three of the patients received retrobulbar lidocaine injections, and one patient (Patient 1) received retrobulbar lidocaine plus epinephrine. In no case was there any evidence of retrobulbar hemorrhage or nonperfusion of the central retinal artery following injection.

Discussion

In all seven patients who experienced profound visual loss following panretinal photocoagulation, the pretreatment fundus appearance showed diffuse marked ischemia with capillary nonperfusion. All patients eventually recovered vision. In all but two patients, visual acuity returned to within two Snellen lines of the pretreatment level. In five patients, visual recovery occurred within 13 weeks.

Huamonte and associates² examined the immediate complications of panretinal photocoagulation and found that choroidal detachments occurred in as many as 100% of patients. Shallow anterior chambers, exudative retinal detachments, and increased intraocular pressure occurred less frequently. These authors did not comment on the visual results of these complications, however.

The Diabetic Retinopathy Study⁶ found the proportion of eyes with early, persistent visual acuity decrease of five or more lines to be about the same for untreated and argon-treated eyes (1.3% and 1.0%, respectively). However, this

TABLE 1
CLINICAL CHARACTERISTICS

PATIENT NO., AGE (YRS), SEX	PREVIOUS PANRETINAL PHOTO- COAGULATION	PRE- TREATMENT VISUAL ACUITY	CAUSE OF DECREASE*	TIME TO DECREASE	VISUAL ACUITY AT DAY DECREASE NOTED [†]	TIME TO RECOVER	VISUAL ACUITY AT RECOVERY	FINAL VISUAL ACUITY
1, 22, M	No	20/100	ON, ME, RI	3 days	HM, later	10 wks	20/120	20/160
					NLP	ę.		
2, 23, M	No	20/16	_	1 day	HM [‡]	6 days	20/25, visual field poor	20/25, visual field improved
3, 38, F	No	20/50	ME	2 days	LP	12 days	20/200	20/50
4, 61, M	No	20/100	ME, RI	1 wk	5/200	3 wks	20/100	20/100
5, 28, F	Yes	20/60	ME	3 wks	2/200	16 wks	20/160	20/60 at 21 mos
6, 31, F	No	20/80	RI	3 wks	3/200	8 wks	20/160	CF
7, 57, F	Yes	20/300	ME, RI	4 wks (gradual)	HM, visual fields poor	8 wks	1/200	1/200

^{*}ME, macular edema; ON, optic neuropathy; RI, retinal ischemia.

study considered only visual loss that persisted at 12 months after treatment and therefore did not examine the type of visual loss experienced by our patients. Doft and Blankenship⁷ prospectively followed up 50 patients who received panretinal photocoagulation in either single or multiple sessions. In their series, 12% of patients lost five or more lines of vision at one week. This percentage decreased to 6% at three weeks and 4% at six months. The cause of

visual loss in these patients was not stated. Bresnick and associates⁸ described two diabetic patients with preexisting severe ischemic changes whose visual acuity decreased sharply immediately after panretinal photocoagulation. Neither patient showed any substantial recovery.

Early visual loss following panretinal photocoagulation can be caused by exudative macular detachments⁷ or macular edema. Two of our

TABLE 2
TREATMENT CHARACTERISTICS

PATIENT NO.	NO. OF LASER SPOTS*	RETROBULBAR INJECTION	PRETREATMENT MACULAR EDEMA	SIGNIFICANT WORSENING OF MACULAR EDEMA AFTER TREATMENT	CHOROIDAL DETACHMENT	SEROUS MACULAR DETACHMENT
1	900	Yes	Yes	Yes	Yes	Yes
	700	Yes			1	
	1,000	Yes				
2	1,000	Yes	No	No	No	No
3	1,401	No	Yes	Yes	Yes	Yes
4	574	No	Yes	No	No	No
5	1,325	Yes	Yes	No	No	No
6	1,230	Yes	No	No	No	No
7	976	No	Yes	No	No	No

^{*}Number of laser spots for each treatment session before visual loss.

[†]HM, hand motions; LP, light perception; NLP, no light perception.

[‡]Reported by patient.

patients (Patients 1 and 3) were noted to have macular edema and shallow exudative macular detachments. In Patient 3, it is unclear whether this was sufficient to account for her loss of vision to the level of light perception. Patient 1 experienced loss of vision to no light perception while his macular detachment decreased. Three other patients showed some evidence of macular edema, and in each of these the examining physician did not judge the macular edema to be significantly worse following treatment. These clinical observations were confirmed by comparison of pretreatment and posttreatment fluorescein angiograms and stereoscopic color photographs. Only one patient (Patient 5) received focal laser treatment for macular edema. This was because all of the patients were treated before the efficacy of focal laser treatment was demonstrated by the Early Treatment Diabetic Retinopathy Study. 10

Severe sudden visual loss during panretinal argon photocoagulation has been associated with peripapillary burns. 11 None of the patients described herein received burns close to the optic nerve.

Choroidal detachments and intraocular pressure increases have been reported after panretinal photocoagulation. 7,12,13 Choroidal detachments were noted in two of our patients. These detachments involved only the peripheral fundus and were not sufficiently bullous to obstruct the visual axis. Although transient increases in intraocular pressure could have occurred between the time of treatment and follow-up examinations, none of our patients was found to have increased intraocular pressure. A shallow anterior chamber was noted in only one case (Patient 3).

There are numerous potential complications of retrobulbar injection.4 Four of our patients received retrobulbar injections before treatment. None of these patients was observed to have signs of retrobulbar hemorrhage. Central retinal artery occlusion following retrobulbar anesthesia has been observed in the absence of retrobulbar hemorrhage,14 but this was not seen either during or after treatment in any of our patients. We cannot exclude the presence of mild optic nerve trauma or optic nerve sheath hematoma as a cause of transient visual loss. 15 However, no patients were observed to have swollen optic nerves or subsequent optic nerve pallor. Although afferent pupillary defects were noted in two patients, their significance cannot be determined in the presence of asymmetric panretinal photocoagulation.

In five of our patients, visual loss could not be accounted for by the observable clinical findings. In a review of 175 eyes treated with panretinal photocoagulation, McDonald and Schatz¹⁶ noted one patient with visual loss of unknown cause, but the degree of loss was not stated. The variable onset and duration of the visual loss described herein suggest that several mechanisms may be at work. The panretinal photocoagulation may have caused changes in blood flow in either the retinal microcirculation or the choroid. Argon laser photocoagulation is known to cause local closure of the choriocapillaris^{17,18} and even larger choroidal vessels. 19 This may result in changes in patterns of choroidal blood flow resulting in temporary ischemia of the posterior pole. The patients in this series may have been particularly sensitive to such changes in blood flow because of their marked preexisting retinal ischemia. Unfortunately, the flattening of both the photopic and scotopic responses in the two patients in whom electroretinography was performed cannot be used to support this concept since reductions in amplitude as high as 95% have been observed following panretinal photocoagulation in patients who did not have visual loss. 20 Since all of our patients had severe retinal vascular disease, the possibility of coincidental fluctuations of macular ischemia not related to photocoagulation cannot be excluded.

Although the cause remains uncertain, both treating physicians and their diabetic patients should be aware of profound, transient visual loss as a potential complication of panretinal photocoagulation.

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OPHTHALMIC MINIATURE

Molecules respond to light as do people to music. There are some who are unaffected and absorb nothing, there are some who react by the degraded vibration of foot or finger, but some there are who rise and dance and change partners. Such a dance of atoms was seen in 1876 when Franz Boll first described the bleaching of rhodopsin.

W. A. H. Rushton, *The Sherrington Lectures, VI. Visual Pigments in Man*Springfield, Charles C Thomas, 1962, p. 3

Paraneoplastic Night Blindness With Malignant Melanoma

Eliot L. Berson, M.D., and Simmons Lessell, M.D.

A 69-year-old hyperopic man developed acute night blindness and hallucinations of shimmering lights three years after resection of a cutaneous malignant melanoma. There were no metastatic ocular lesions and he had received no medications. His electroretinogram showed abnormalities comparable to those of patients with congenital stationary night blindness with myopia. Metastatic melanoma was recognized several months later. His electroretinographic responses were also identical to those ascribed to vincristine therapy in a previously described patient with malignant melanoma. Our findings showed that acquired night blindness, apparently resulting from interruption of intraretinal rod signal transmission, can be a paraneoplastic effect of a malignant melanoma.

Patients with congenital stationary night blindness with myopia, inherited by an X-linked or autosomal recessive mode, show a characteristic cornea-negative electroretinographic response under dark-adapted conditions and normal cone electroretinographic amplitudes under light-adapted conditions. ¹⁻⁹ Ripps and associates ^{10,11} reported identical wave forms in a patient with malignant melanoma who suddenly developed night blindness. They ascribed the retinopathy to the patient's vincristine therapy. Herein we describe the findings in a patient with malignant melanoma who suddenly developed night blindness. His electroretinographic abnormalities

resembled those seen in patients with congenital stationary night blindness with myopia. Since the patient had received no treatment before the onset of visual symptoms or the recording of his electroretinogram, we present this case as evidence that this patient's retinal malfunction must represent a paraneoplastic effect of the melanoma.

Case Report

A 69-year-old man suddenly noticed that he was night blind when he went from a brightly lit room into a dark closet on Nov. 22, 1985. From that time he also reported hallucinations of pulsating, shimmering lights. The lights were large (transparent "blobs") in dim surroundings and seemed to further impair his vision but were much smaller in bright surroundings. Because of these symptoms he could no longer drive at night. He had enjoyed good vision and had served as a night watch on a ship during World War II. There was no family history of night blindness or other ocular disease.

The patient had been in good health until March 1983 when a melanoma of the superficial spreading type, level III, was widely excised from the right anterior abdominal wall. In May 1986, six months after the onset of visual symptoms, another mass identified in his right axilla was found to be a malignant melanoma.

In April 1986, visual acuity with spectacle correction (+1.50 sphere in both eyes) was R.E.: 20/25 and L.E.: 20/20. The patient reported that his vision seemed to fluctuate from moment to moment during the testing. Goldmann visual fields were full to the III_{4e} white stimulus. It was impossible to test with the I_{4e} or smaller stimuli because the lights that he hallucinated were the same size and caused confusion. Results of slit-lamp examination and ophthalmoscopy were unremarkable. Intraocular pressure by applanation tonometry was 12 mm Hg in both eyes. Results of color vision testing on the Farnsworth D-15 panel

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and Ishihara plates were normal. After 45 minutes of dark adaptation, the patient's threshold to an 11-degree white test light fixated 7 degrees above the fovea in a dark adaptometer was increased 3 log units above normal in both eyes; comparable increases were reported when the patient viewed the test light in extreme positions of gaze. Thresholds were also increased 3 log units after 12 hours of patching of one eye. Fluorescein angiograms showed occasional window defects in the retinal pigment epithelium but were otherwise unremarkable. Normal results were obtained on a complete blood cell count, urinalysis, serum retinol determination, serum amino acid level determination, and liver function tests.

Full-field electroretinograms were monitored with a double-electrode contact lens placed on the topically anesthetized cornea, differentially amplified at a gain of 1,000 (-3 dB at 2 Hz and 300 Hz), and photographed from an oscilloscope. Each eye was tested after maximal pupil dilation with 10% phenylephrine hydrochloride and 1% cylopentolate hydrochloride and 45 minutes of dark adaptation. Responses were first recorded to single flashes (0.5 Hz) of dim blue light (-3.8 log ft-L-seconds, $\lambda_{max} = 440 \text{ nm}$, a rod-isolated response) and then 0.5-Hz flashes of red light (-1.8 log ft-L-seconds, $\lambda_{50\%}$ cut-on = 605 nm, a mixed cone and rod response) that was matched in brightness to the blue light for the rods, so that any component of the electroretinogram elicited by the red light and not the blue light could be attributed to remaining cone function. Then electroretinograms were recorded to 0.5-Hz white light (-0.8 log ft-Lseconds, a mixed cone and rod response) and 30-Hz white flickering light (−1.2 log ft-Lseconds, a cone-isolated response). Stimulus flash duration was 10 µsec for each condition. Responses were quantitated with respect to peak-to-peak amplitude and compared with representative normal subjects and patients with congenital stationary night blindness with myopia. Electroretinograms were first evaluated in June 1986 and were reevaluated in July 1986 after overnight patching of one eye to see if amplitudes increased after 12 hours of dark adaptation.

In October 1986, the patient developed an axillary infection requiring hospitalization for intravenous antibiotic therapy; this prevented further ophthalmologic investigations. He became anorexic and was treated symptomatically until early January 1987 when he received a

course of intravenous dacarbazine. A few weeks later, he died of pulmonary metastases and renal failure. An autopsy was not performed.

Results

We compared full-field electroretinographic responses from both eyes of our patient with representative normal responses and responses from a patient with congenital stationary night blindness with myopia (Figure). Our patient with melanoma and acquired night blindness showed no detectable rod responses to matched blue and red light stimuli, consistent with the inability of the rod system to generate a b-wave; the patient did retain a small corneapositive oscillation to red light from the cone system in each eye. In contrast to normal, our patient showed only a cornea-negative a-wave from the cone and rod photoreceptors to single flashes (0.5 Hz) of white light under darkadapted conditions, whereas cone amplitudes to 30-Hz white flickering light were comparable to normal. His responses resembled those of a representative patient with congenital stationary night blindness with myopia (Figure).

Results of repeat electroretinography in our patient one month later were identical to those shown in the Figure, and no increase in amplitudes was observed after 12 hours of dark adaptation.

Discussion

In 1984, Ripps and associates¹¹ described a 30-year-old man with a cutaneous malignant melanoma and a history of acute onset of pulsating, flashing lights and acquired night blindness. His electroretinogram showed a nondetectable rod response to blue light, a cornea-negative a-wave from the photoreceptors to white light, and normal peak-to-peak cone amplitudes to single flashes of white light on a background. This patient also had normal rhodopsin kinetics as monitored by fundus reflectometry and spectral sensitivity functions comparable to those previously described for hereditary forms of congenital stationary night blindness with myopia. Our patient gave the same history of flickering or shimmering lights

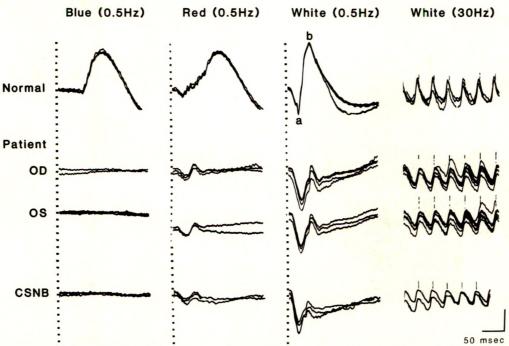


Figure (Berson and Lessell). Full-field electroretinographic responses from a normal subject, from the right (OD) and left (OS) eyes of a patient with malignant melanoma, and from a patient with congenital stationary night blindness with myopia (CSNB). Stimulus onset is designated by the vertical hatched lines in columns 1, 2, and 3 and the vertical lines superimposed on the responses in column 4. Two or three consecutive responses are illustrated and cornea positivity is an upward deflection. The peak of the cornea-negative a-wave, generated by photoreceptors, and the peak of the cornea-positive b-wave, generated by activity of cells proximal to the photoreceptors, are designated in the response of the normal subject to single flashes of white light. Lower right, Calibration symbol designates 50 msec horizontally, 200 μV vertically for the top recording in column 3, and 100 μV vertically for all other tracings. Both patients lack the cornea-positive b-wave from the rod system in columns 1, 2, and 3 in contrast to the normal while retaining normal cone amplitudes (≥50 μV) in their responses to 30-Hz white flickering light in column 4.

with sudden onset of night blindness and had electroretinographic responses identical to those reported by Ripps and associates. This supports the proposal that cutaneous malignant melanoma can be associated with an acquired defect in intraretinal transmission of rod responses such that the rods generate an a-wave but more proximal retinal neurons do not respond.

A major difference between this previously reported case and our case was that the former patient developed symptoms after he received vincristine chemotherapy. Since vincristine is known to disrupt the structural integrity of neuronal microtubules¹²⁻¹⁵ and since electroretinographic responses similar to those found in these patients can be obtained when vincristine

is perfused in an isolated perfused eye preparation, it was reasonable to assume that vincristine chemotherapy contributed to the development of the night blindness in that patient. Dur patient suffered from acquired night blindness and had abnormal results on electroretinography one year before he was given any chemotherapy, suggesting that either the melanoma itself, some substance released by the melanoma, a circulating antibody to some protein in the melanoma, or some combination of these factors may have modified intraretinal transmission of the rod responses.

In their original report of a paraneoplastic photoreceptor degeneration, Sawyer and coworkers¹⁶ included the case of a woman with metastatic oat cell bronchogenic carcinoma

who complained of night blindness and episodic visual hallucinations, including "gold, flickering specks... that shimmered...," but electroretinographic findings were not reported. A review of reported cases of paraneoplastic photoreceptor degeneration indicates that electroretinographic responses were either not recorded, were extinguished with the loss of both a- and b-waves, or showed rod responses larger than the cone responses, unlike the waveforms reported here. 17-19 The association of carcinomas with compromised retinal function highlights the importance of searching for occult malignancies in patients with acquired night blindness and abnormal electroretinographic findings who have no other ocular explanation for difficulty seeing or driving at night, such as cataracts, glaucoma treated with miotics, uncorrected myopia, macular degeneration, or retinitis pigmentosa.

Paraneoplastic manifestations have been recorded in patients with malignant melanoma. These include dermatomyositis, melanosis syndrome (diffuse cutaneous hyperpigmentation and dark urine), vitiligo, halo nevi, cachexia, the "hot spleen" phenomenon (in which the spleen accumulates more technetium-99m sulfur colloid isotope than the liver, a reversal of the normal pattern), hypercalcemia from parathormone secretion by the tumor, Cushing's syndrome from adrenocorticotropic hormone production by the tumor, disseminated intravascular coagulation, and the eosinophilic leukemoid reaction. 20 Several paraneoplastic cutaneous manifestations, including acanthosis nigricans, multiple skin tags, and multiple seborrheic keratoses, were recently described in a patient with a nonmetastatic malignant melanoma of the skin.21

Neural tissue such as the retina has never before been implicated in paraneoplastic manifestations of malignant melanoma. The precise mechanism by which a melanoma causes interruption of intraretinal rod signal transmission and acquired night blindness is yet to be identified. Unlike other forms of stationary night blindness associated with either a defect in neural adaptation proximal to the photoreceptors (Oguchi's disease) or a defect in visual pigment regeneration by the photoreceptors (fundus albipunctatus), our patient did not improvement in final darkshow any adaptation threshold or electroretinographic amplitude after 12 hours of dark adaptation. Excised tumor or serum from future patients who have malignant melanoma with acquired

night blindness might be used in physiologic, autoradiographic, and immunocytochemical studies to identify substances that might be causing defective intraretinal conduction as well as congenital stationary night blindness with myopia.

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OPHTHALMIC MINIATURE

Reverend R. J. E. Boggis, in a Letter to the Editor of the *Times of London*, Feb. 1, 1946:

A correspondent of the Manchester Sporting Chronicle, thinking that his horse was shortsighted, had his eyes examined by an oculist, who certified that the horse had a No. 7 eye, and required concave glasses. These were obtained and fitted on to the horse's head. At first the horse was a little surprised, but rapidly shewed signs of the keenest pleasure, and he now stands all the morning, looking over the half-door of his stable with his spectacles on, gazing around him with an air of sedate enjoyment; when driven his manner is altogether changed from his former timidity, but if pastured without his spectacles on he hangs about the gate whinnying in a plaintive minor key. If the spectacles are replaced he kicks up his heels and scampers up and down the pasture with delight.

Your Obedient Servant, Edited by Kenneth Gregory London, Times Newspapers Ltd. and George Allen & Unwin Ltd., 1976, p. 203

Long-Term Reduction of Intraocular Pressure After Repeat Argon Laser Trabeculoplasty

Douglas K. Grayson, Sc.B., Carl B. Camras, M.D., Steven M. Podos, M.D., and Jacqueline S. Lustgarten, M.D.

Thirty-eight eyes (in 31 patients with glaucoma) that had shown a favorable response to an initial argon laser trabeculoplasty had a repeat laser trabeculoplasty four to 81 months (mean \pm S.E.M., 23 \pm 3 months) later because of inadequately controlled intraocular pressures. A mean (\pm S.E.M.) of 65 \pm 3 burns (range, 50 to 115) were given during the initial laser trabeculoplasty, and 58 ± 2 burns (range, 36 to 100) were given during the first repeat treatment. Three months after the first repeat laser trabeculoplasty, one eye (3%) had undergone filtering surgery and 30 eyes (78%) were considered successes. Of the 30 eyes that were followed up for 12 months after the first repeat laser trabeculoplasty, two (7%) had undergone filtering surgery, three (10%) had received a second repeat laser trabeculoplasty, and 22 (73%) were successes. Fifteen eyes underwent a second repeat laser trabeculoplasty at six to 47 months (mean \pm S.E.M., 21 \pm 3 months) after the first repeat laser trabeculoplasty. Seven (47%) of these eyes required filtering surgery within three to 12 months after the second repeat laser trabeculoplasty. Four of 38 (11%) of the initial, two of 38 (5%) of the first repeat, and zero of 15 of the second repeat laser trabeculoplasty treatments resulted in a one- to two-hour rise in intraocular pressure of at least 10 mm Hg.

It is unclear whether argon laser trabeculoplasty is effective in avoiding filtering surgery or whether it merely postpones a filtering operation. Several reports have shown that after an initial treatment, intraocular pressure is lowered, but then slowly climbs over a period of several months to years to a level at which surgical intervention becomes necessary. ¹⁻⁴ Recently, several studies have examined the results of repeat sessions of laser trabeculoplasty and concluded that few patients had significant reductions of intraocular pressure that were maintained for longer than several months. ⁵⁻⁸ Some patients even showed a sustained rise in intraocular pressure, necessitating emergent filtering surgery. ^{5,6}

In light of the many potential complications of filtering surgery, including reduced visual acuity, hypotony, cataracts, intraocular hemorrhage, and infection, all of which are avoidable with laser trabeculoplasty, it is important to determine whether or not a patient can benefit from repeat laser trabeculoplasty if the intraocular pressure rises again to a level that is inconsistent with preservation of visual function. Herein we present the results of our experience with repeat laser trabeculoplasty treatments.

Subjects and Methods

We reviewed the records of all patients in our practice who had undergone laser trabeculoplasty. A repeat laser trabeculoplasty was defined as additional treatment given at least four months after an initial session, regardless of the number of spots applied each time. Although the patient population studied with a repeat laser trabeculoplasty is somewhat disparate from the point of view of number of spots given initially, we felt justified in grouping the patients for part of our analysis as they all had in common a successful treatment of at least four months' duration. Only those patients who demonstrated an initial hypotensive re-

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sponse to the first treatment were considered candidates for repeat laser trabeculoplasty. A total of 38 eyes in 31 patients qualified by these criteria.

All patients were taking maximally tolerated ocular hypotensive medications, which usually included a beta-blocker, a cholinergic agent, an adrenergic agent, and a carbonic anhydrase inhibitor, at the time of the laser trabeculoplasty, and had intraocular pressures that were considered too high for preservation of visual field. In addition to their maximally tolerated ocular hypotensive medications, some patients were treated with orally administered hyperosmotic medications just before their laser trabeculoplasty session, including three of 38 patients undergoing initial laser trabeculoplasty, seven of 38 undergoing the first repeat treatment, and two of 15 undergoing the second repeat treatment. Generally, these patients had marked glaucomatous visual field loss approaching central fixation.

Any given laser teatment was administered to either 360 degrees or 180 degrees of the anterior trabecular meshwork at the junction of the nonpigmented and pigmented regions. A three-mirror Goldmann contact lens was used in conjunction with the argon laser set for a spot size of 50 µm and an exposure duration of 0.1 second. Power level ranged from 800 to 1,200 mW, depending on the amount of pigment in the trabecular meshwork, with the desired effect being either blanching of the pigment or the formation of a small bubble. Sites of previous laser treatments were not used as a guide to place spots in subsequent treatment sessions, since often they could not be distinguished. However, if only 180 degrees were treated in an initial session, the opposite 180 degrees were treated in a subsequent ses-

A pretreatment intraocular pressure value was calculated as the average of all intraocular pressures taken in the one-month interval preceding the laser trabeculoplasty. Intraocular pressures were recorded at the following intervals after each repeat laser trabeculoplasty: one to two hours (single peak value); one-half to one month; three months \pm one week; six months \pm one week; 12 months \pm one week; 18 months \pm one week; 24 months \pm one week; and 30 months \pm one week. The value at any time period after laser trabeculoplasty represented an average intraocular pressure of all measurements taken within the specified interval. The number of eyes at each time interval

decreased for three reasons: (1) some eyes underwent filtering surgery; (2) some underwent a second repeat laser trabeculoplasty, placing them in another group for analysis; or (3) some had not yet been followed up to that interval after the repeat laser trabeculoplasty.

Success was defined by the following four criteria: (1) either a 15% drop in intraocular pressure as compared to the pretreatment value or an intraocular pressure below 21 mm Hg; (2) no filtering procedures; (3) no further repeat laser trabeculoplasties; and (4) no progressive visual field loss or increase in cup/disk ratio. A second repeat laser or filtering surgery was performed if a given eye had intraocular pressures that were considered too high for preservation of visual field. Of the two eyes that underwent filtering surgery before a second repeat laser trabeculoplasty was attempted, one had an intraocular pressure as high as 47 mm Hg and the other had rapidly progressive visual field loss despite only moderately increased intraocular pressures.

A paired *t*-test was used to compare the intraocular pressure at a given time interval after the repeat laser trabeculoplasty to the pretreatment intraocular pressure. Further analysis included the determination of the minimum intraocular pressure (excluding the first week after treatment) attained after both the initial and repeat laser trabeculoplasties, and when this maximal reduction occurred. A comparison was also made of the intraocular pressure just before each initial and repeat laser treatment, and the peak intraocular pressure measured one to two hours afterward.

Of these 38 eyes, 17 had repeat laser trabeculoplasties after receiving at least 90 burns distributed over 360 degrees in one or two previous sessions. In addition to their evaluation in the overall group of 38 eyes, these 17 eyes also were analyzed separately since 90 to 110 burns can be considered an initial treatment regardless of the time intervals between sessions to accumulate this number of burns.

Results

The study included 17 men and 14 women who ranged in age from 32 to 88 years (mean \pm S.E.M., 67.8 \pm 2.3 years). Twenty-five patients were white and six were black. Most patients had phakic primary open-angle glaucoma (Table 1). Of the 38 eyes, only four had an

TABLE 1
OCULAR CHARACTERISTICS

CHARACTERISTICS	NO. OF EYES (N=38)
Diagnosis	(11 30)
Primary open-angle glaucoma	32
Exfoliation glaucoma	4
Pigmentary glaucoma	2
Lens status	
Phakic	31
Aphakic	5
Pseudophakic	2

initial laser trabeculoplasty for 180 degrees, whereas the remaining 34 had burns applied for 360 degrees. There was an average interval of approximately two years between the initial and the first repeat laser trabeculoplasty, and again between the first and second repeat laser trabeculoplasty (Table 2).

Of the 38 eyes, 15 (39%) underwent a second repeat laser trabeculoplasty an average of 21.2 ± 3.2 months after the first repeat trabeculoplasty (Table 2). At 3.0 and 3.3 months after the first repeat laser trabeculoplasty, two (5%) of the original 38 eyes had undergone filtering

surgery without a second repeat laser trabeculoplasty. By 12 months after the second repeat laser trabeculoplasty, seven of 15 eyes (47%) had undergone filtering surgery. Of those eyes not undergoing surgery, a significant (P < .05) decrease in intraocular pressure occurred at one-half to one, three, six, 12, and 18 months after the first repeat laser trabeculoplasty, and at three months after the second (Fig. 1, top).

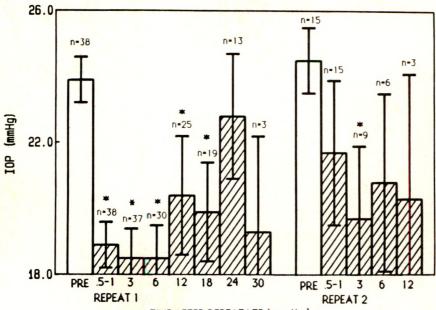
Of the 17 eyes that underwent a repeat laser trabeculoplasty after receiving at least 90 previous burns, five underwent a second repeat trabeculoplasty an average of 24 ± 7 months after the first (Table 2). By 12 months after the first repeat laser trabeculoplasty, five (29%) of the original 17 eyes had undergone filtering surgery without a second repeat laser trabeculoplasty. At one and seven months after the second repeat treatment, two of these five eyes underwent filtering surgery. Of those eyes not undergoing filtering surgery, there was a significant (P < .05) decrease in intraocular pressure at three, six, 12, 18, and 24 months after the first repeat laser trabeculoplasty, and at one-half to one month after the second (Fig. 1,

In the main group of 38 eyes, more than 70% of the eyes were considered successes at one-half to one, three, six, 12, and 18 months after the first repeat treatment, and greater than 40%

TABLE 2

NUMBER OF PHOTOCOAGULATION BURNS AND INTERVALS BETWEEN EACH ARGON LASER TRABECULOPLASTY

FACTOR	INITIAL TREATMENT		FIRST REPEAT TREATMENT		SECOND REPEATMENT
All Eyes					
No. of eyes	38		38		15
No. of photocoagulation	65.0 ± 3.2		57.8 ± 1.9		53.6 ± 2.9
burns (mean ± S.E.M.)					
Range	50-115		36-100		33-70
Time interval between		23.0 ± 3.0		21.2 ± 3.2	
treatments (mos)					
(mean ± S.E.M.)					
Range		4.0-81.3		6.0-47.5	
Eyes With ≥ 90 Burns Before Repeat L	aser Trabeculoplasty				
No. of eyes	17		17		5
No. of photocoagulation	112.8 ± 5.2		57.4 ± 2.9		48.6 ± 4.3
burns (mean ± S.E.M.)					
Range	93-143		33-70		35-60
Time interval between		24.9 ± 3.5		24.2 ± 7.3	
treatments (mos)					
(mean ± S.E.M.)					
Range		6.8-59.8		6.0-47.5	



TIME AFTER REPEAT LTP (months)

* p<0.05 as compared to pretreatment value

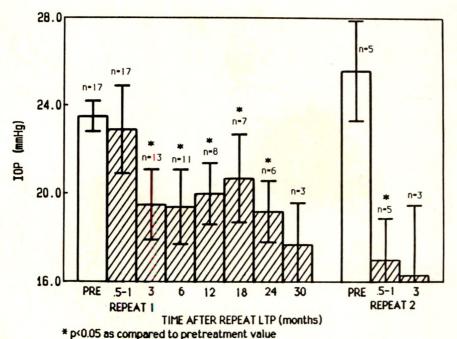
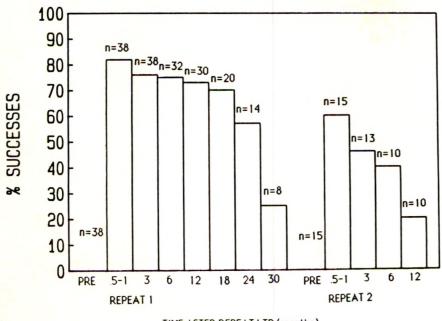


Fig. 1 (Grayson and associates). Mean ± S.E.M. intraocular pressure (IOP) after repeat argon laser trabeculoplasty (LTP) over time. Top, All eyes; bottom, eyes with 90 or more initial burns. N indicates no. of eyes.

at one-half to one, three, and six months after the second repeat treatment (Fig. 2, top). In the subgroup of 17 eyes, 40% to 65% were successes at six, 12, 18, 24, and 30 months after the first repeat laser trabeculoplasty, and more than 75% at one-half to one and three months after the second repeat trabeculoplasty (Fig. 2, bottom); however, only nine of the 17 eyes were

followed up for 18 months, six for 24 months, and five for 30 months after the first repeat treatment, and only five eyes underwent a second repeat treatment. The mean minimum intraocular pressure reached after each laser trabeculoplasty ranged from 14 to 17 mm Hg. It occurred at a mean of four to six months after the initial laser trabeculoplasty, and at two to



TIME AFTER REPEAT LTP (months)

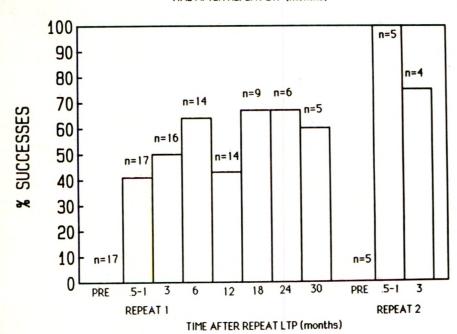


Fig. 2 (Grayson and associates). Success rates after repeat argon laser trabeculoplasty (LTP) over time. Top, All eyes; bottom, eyes with 90 or more initial burns. N indicates no. of eyes.

four months after each repeat laser trabeculoplasty (Table 3).

The mean peak intraocular pressure occurring one to two hours after each laser trabeculoplasty showed no significant increase, because some eyes showed pronounced decreases in intraocular pressure, whereas others showed increases. Four eyes after the initial, two eyes

after the first repeat, and no eyes after the second repeat laser trabeculoplasty showed at least a 10-mm Hg increase in intraocular pressure at one to two hours (Fig. 3, top). Similar results were obtained in the subgroup of eyes with an initial 90 or more burns (Fig. 3, bottom). No eyes required emergency filtering surgery.

MINIMUM INTRAOCULAR PRESSURE* AND TIME OF OCCURRENCE AFTER ARGON LASER TRABECULOPLASTY (MEAN ± S.E.M.)

LASER TRABECULOPLASTY	ALL EYES	EYES ≥ 90 INITIA
Initial treatment		
No. of eyes	38	17
Minimum intraocular	14.4 ± 0.5	13.6 ± 0.7
pressure (mm Hg)		
Range	8.0-20.0	8.0-20.0
Time after that minimum	6.2 ± 1.6	4.6 ± 2.0
intraocular pressure		,
occurred (mos)		
Range	0.3-40.0	0.3-33.0
First repeat treatment		
No. of eyes	38	17
Minimum intraocular	13.9 ± 0.5	16.8 ± 1.7
pressure (mm Hg)		
Range	8.0-20.0	11.0-13.0
Time after that minimum	3.9 ± 0.7	2.1 ± 0.4
intraocular pressure		
occurred (mos)		
Range	0.3-16.0	0.3-6.0
Second repeat treatment		
No. of eyes	15	5
Minimum intraocular	16.9 ± 2.0	14.0 ± 2.2
pressure (mm Hg)		
Range	9.0-37.0	5.0-22.0
Time after that minimum	2.2 ± 0.9	3.2 ± 2.4
intraocular pressure		
occurred (mos)		
Range	0.3-13.0	0.3-13.0

^{*}Minimum intraocular pressure is the lowest pressure recorded after each argon laser trabeculoplasty.

Discussion

An initial laser trabeculoplasty effectively reduces intraocular pressure in some patients on maximally tolerated medication. 2,4,9-14 However, it is uncertain whether patients can further benefit by repeat laser trabeculoplasty before filtering procedures. Previous studies have concluded that few patients benefit from repeat laser trabeculoplasties, 5-8 and some even have adverse increases in intraocular pressures requiring urgent filtering surgery (Table 4). 5,6

In a previous study of 17 eyes that had generally shown a poor response to an initial

laser trabeculoplasty and underwent repeat laser trabeculoplasties, 53% of eyes had a reduction in intraocular pressure greater than or equal to 3 mm Hg at an average follow-up period of three months.5 Using similar success criteria, another study demonstrated that 32% of the eyes had at least a 3-mm Hg decrease in intraocular pressure at an average follow-up interval of eight months.8 In a third study, 38% of the eyes had reductions in intraocular pressure sufficient to avoid filtering surgery after an average follow-up period of 5.2 months. 6 A fourth study showed that 36% of the eyes had at least a 15% reduction in intraocular pressure at six weeks; only 21% of the eyes had such a reduction six months after the repeat laser trabeculoplasty.7 Using a sample size of 38 eyes, we examined only those eyes that had shown a favorable response to the initial laser treatment; otherwise, repeat laser trabeculoplasty would not have been performed. With a longer follow-up time (up to 30 months), and evaluation of both first and second repeat laser trabeculoplasties, the present study showed that of the 30 eyes followed up for 12 months after the first repeat laser trabeculoplasty, 73% were considered successes as defined in the Subjects and Methods section (Table 4). Of the ten eyes followed up for six months after the second repeat laser trabeculoplasty, four were successes.

Whereas previous studies found 29% to 62% of eyes required filtering surgery after repeat laser trabeculoplasties, 5-8 only two of 38 eyes (5%) after the first repeat laser trabeculoplasty and seven of 15 eyes (47%) after the second repeat trabeculoplasty required such surgery in the present study after a longer follow-up period. Factors that have been shown to influence the extent of intraocular pressure reduction and success rate following laser trabeculoplasty include the pretreatment level of intraocular pressure, 15,16 patient age, type of glaucoma, and lens status (phakic or aphakic). 15 These factors were similar among the previously reported studies 5-8 and the present one.

It is difficult to determine the relative effect of different treatment parameters among the studies to account for the varying effect on intraocular pressure and success rate, because the number of photocoagulation burns were specified in only one⁷ of the repeat laser trabeculoplasty studies previously reported. The laser treatment parameters may have influenced the relative success rate of the proce-

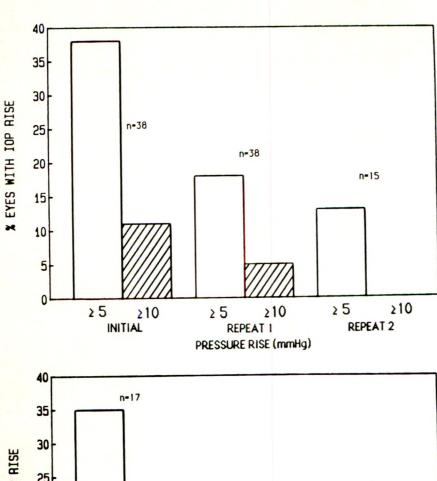
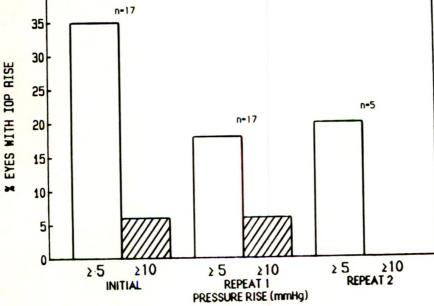


Fig. 3 (Grayson and associates). Percentage of eyes with intraocular pressure (IOP) rise one to two hours after repeat laser trabeculoplasty. Top, All eyes; bottom, eyes with 90 or more initial burns. N indicates no. of eyes.



dure. It may be speculated that the number of initial burns is a key factor in the success of repeat laser trabeculoplasty. In the four previous studies discussed, 5-8 the initial treatment always consisted of laser burns to either 360 degrees in one session or to 180 degrees in two sessions; it is most likely that the total number of initial burns in these studies was approximately 100. In the present study, the 17 eyes

that had an initial treatment of at least 90 burns demonstrated a success rate of 64% at six months and 43% at 12 months after repeat laser trabeculoplasty, which is comparable to the findings of the previous studies. However, in our main group of 38 eyes, most eyes were given an initial treatment of approximately 65 burns, and a success rate of 73% at 12 months after the first repeat laser trabeculoplasty was

TABLE 4
COMPARISON OF REPEAT ARGON LASER TRABECULOPLASTY STUDIES

STUDY	NO. OF EYES	DEGREES INITIAL	MEAN NO. OF BURNS INITIAL (RANGE)	MEAN NO. OF MONTHS BETWEEN INITIAL & REPEAT (RANGE)	DEGREES REPEAT	MEAN NO. OF BURNS REPEAT (RANGE)	SUCCESS RATE OF REPEAT (%)	MEAN FOLLOW-UP FOR SUCCESS RATE AFTER REPEAT (MOS)	IMMEDIATE SPIKE AFTER REPEAT (%)
Starita and associates ⁵	17	360 or 180 ×2	?	9	360	?	35	3	18
Brown and associates ⁶	26	360 or 180 ×2	?	16 (2–42)	180 or 180 ×2	?	38	5	12
Messner and associates ⁷	14	360 or 180 ×2	82 (65–105)	26	360	58 (50–82)	21	6	0
Richter and associates ⁸	40	360 or 180 ×2	?	32	180	50	32	8	0
Present study*	38	360 or 180	65 (50–115)	23 (4–81)	360 or 180	58 (36–100)	75 [‡] 73 [‡]	6 [‡] 12 [‡]	0
Present study [†]	17	360 or 180 ×2	113 (93–143)	25 (7–60)	360	57 (33–70)	64 [‡]	6 [‡]	0

^{*}Eyes that underwent repeat treatment at least four months after an initial treatment, regardless of the number of burns applied.

realized. Thus, it is possible that fewer initial burns may be an important prognostic indicator for the success of repeat laser trabeculoplasties. Even though eyes in our study received fewer burns during the initial treatment, the interval between the initial and the first repeat treatment (23 months) compares favorably with those reported in other studies,5-8 suggesting that our eyes did at least as well with fewer initial burns (Table 4). Although other studies 14,17-19 conclude that application of fewer photocoagulation burns in an initial laser trabeculoplasty treatment session produces a similar short-term reduction of intraocular pressure as the standard 100 burns, none of these evaluated the long-term efficacy. Our results suggest that fewer initial burns (mean, 65) may be as efficacious in the long-term, and may increase the success rate of repeat laser trabeculoplasty, compared with an initial 100 burns.

The incidence of transient intraocular pressure increases of at least 10 mm Hg within several hours after repeat laser trabeculoplasty has been reported to occur in none, 7,8 12%, 6 and 18% of eyes in previous studies. The present study showed an adverse intraocular pressure spike of at least 10 mm Hg in only 11% of eyes following the initial, 5% following the first

repeat, and none following the second repeat laser trabeculoplasty. Perhaps fewer intraocular pressure spikes occurred in the present study because we were less apt to proceed with a repeat laser trabeculoplasty if a significant and deleterious spike occurred after the initial laser trabeculoplasty. Furthermore, compared with other studies, an adverse intraocular pressure spike may have been minimized in the present study by applying fewer burns in the repeat sessions, or by the liberal use of hyperosmotic agents to prevent the increase. Unfortunately, in the previous studies in which intraocular pressure spikes in the immediate postlaser period were observed,5,6 the precise number of burns used in each treatment was not reported, making a comparison of this treatment factor to the present study impossible (Table 4).

In describing a slightly different approach to laser treatment for open-angle glaucoma following failure of an initial laser trabeculoplasty, one group reported the use of a Qswitched Nd:YAG laser to treat the trabecular meshwork and reduce intraocular pressure. ^{20,21} Based on the results of the present study, it is conceivable that many of these same patients may have benefited from repeat argon laser

[†]Eyes that underwent repeat treatment after receiving at least 90 burns over 360 degrees.

[‡]Top success rate corresponds to top follow-up time and bottom rate to bottom time.

trabeculoplasty instead. A prospective, randomized, controlled study is needed to determine the most worthwhile approach to achieve a pronounced and sustained reduction of intraocular pressure following failure of an initial laser trabeculoplasty.

The mechanism by which either argon or Nd:YAG laser procedures reduce intraocular pressure is unclear. Nd:YAG laser treatment is not expected to contract tissue and mechanically open spaces in the posterior trabecular meshwork, as has been postulated for argon laser trabeculoplasty.11 Laser treatment with either argon or Nd:YAG laser to ocular tissues has been shown to stimulate prostaglandin synthesis. 22-25 Human trabecular meshwork cells in tissue culture produce high levels of prostaglandins,26 which are potent ocular hypotensive agents. 27,28 Laser-induced stimulation of local prostaglandin synthesis may be responsible for the intraocular pressure reduction with both types of lasers. 25,29

Based on the results of the present study, we strongly recommend consideration of a repeat laser trabeculoplasty in those patients with an initial beneficial effect following their first treatment. Repeat laser trabeculoplasty can result in a reduction of intraocular pressure for as long as 30 months in some patients. However, many patients will eventually require filtering procedures after undergoing a third (second repeat) laser trabeculoplasty.

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OPHTHALMIC MINIATURE

In order to move, the parts of the sentence skeleton must be properly jointed, articulated; the muscles and connective tissue must be strong and inserted at the right places; the burden of ideas must not be too great for the structure. And to cover all this machinery and make it pleasing, the surface must be reasonably varied and polished.

Jacques Barzun and Henry F. Graff, The Modern Researcher, 1957

Progressive Visual Loss Caused by an Arachnoidal Brain Cyst in a Patient With an Optic Nerve Coloboma

Lisa F. Rosenberg, M.D., and Ronald M. Burde, M.D.

We examined a patient with a known coloboma of the optic nerve head who developed progressive visual loss. Documentation of the optic nerve dysfunction included decreased visual acuity, severe visual field loss, and the presence of an afferent pupillary defect. Highresolution computed tomography showed an arachnoidal brain cyst compressing the involved optic nerve.

CONGENITAL DEFECTS of the optic nerve head occur either in isolation or in association with other congenital ocular or central nervous system anomalies. Such congenital defects include hypoplastic disk, optic nerve pit, coloboma of the optic nerve head, morning glory syndrome, optic nerve dysplasia, and megalopapilla. Affected patients may have normal to severely compromised visual function, but the deficit, if it exists, is nonprogressive. We examined a patient with an anomalous optic nerve who experienced progressive visual loss caused by a coexisting central nervous system lesion at age 45 to 50 years.

Case Report

A 56-year-old woman had been followed up by her ophthalmologist for more than 20 years. Visual acuity was originally 20/20 in both eyes and she had a congenitally excavated nerve head of the right eye. In 1966 a kinetic visual field of the right eye had demonstrated a defect extending inferiorly from the blind spot. She was examined in 1979 by a retinal specialist because of the onset of "flashes"; at that time visual acuity was 20/40 in the right eye. In February 1985 she complained of pain in her right eye. Visual acuity was R.E.: 20/60 and L.E.: 20/20, but no cause was found for the decreased vision on the right. One year later she returned to her ophthalmologist noting an intermittent "film" over the right eye and occasional double vision. Visual acuity was 20/50 in the right eye. Results of kinetic visual fields were unchanged. She was referred for neuroophthalmologic consultation.

When we saw the patient in December 1986, best-corrected visual acuity was R.E.: 20/200 and L.E.: 20/25. A conspicuous right afferent pupillary defect was present. Ocular ductions were full. A large angle intermittent right exotropia was noted. Slit-lamp examination showed minimal posterior subcapsular cataracts, and applanation pressures measured with a Goldmann tonometer were R.E.: 16 mm Hg and L.E.: 20 mm Hg. Results of ophthalmoscopy on the left were normal. The right fundus showed a colobomatous excavation of the optic nerve head located centrally, with inferior extension (Fig. 1) and marked loss of nerve fiber layer. Kinetic visual fields demonstrated a relative central scotoma and advanced nerve fiber bundle defects isolating an inferotemporal island on the right (Fig. 2); the left field was normal. This was a marked change from the results of her previous visual field examination.

Although the appearance of the patient's optic disk anomaly could have been compatible with her visual acuity, the patient's records from her referring ophthalmologist and the retinal specialist clearly demonstrated progressive visual dysfunction. A high-resolution computed tomogram of the orbits was obtained, with particular attention paid to the prechiasmatic optic nerve. A large, low-density fluid collection anterior to the right temporal lobe in the right middle cranial fossa was found and thought to be consistent with an arachnoid

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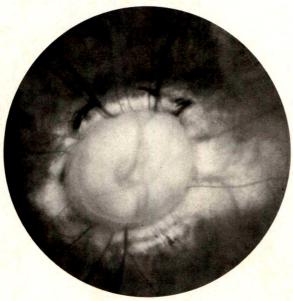


Fig. 1 (Rosenberg and Burde). Colobomatous right disk. No nerve fiber bundle striations present.

cyst. The cyst caused inward bowing of the posterolateral wall of the right orbit. Focal hypoplasia of the right temporal lobe and right frontal cortex was present (Fig. 3).

On Feb. 17, 1987, the patient underwent a right temporal craniotomy, which confirmed the presence of a large arachnoid cyst. The cyst was evacuated and subtotally resected.

Postoperatively the patient's visual acuity remained 20/200 in the right eye. Results of repeat kinetic perimetry remained unchanged.

Discussion

The term coloboma, derived from Greek, means curtailed or mutilated. This malformation results from failure of closure at the most proximal portion of the optic stalk anytime between two and eight weeks of gestation. Coloboma of the optic disk may be isolated or associated with chorioretinal coloboma. The optic nerve often appears as an enlarged and excavated disk, without tissue at the base of the defect. The coloboma may involve all or only part of the disk substance. The retinal vessels have an abnormal origin. Optic nerve head colobomas may occur bilaterally but may be asymmetric.

Other congenital anomalies of the optic nerve head demonstrate a different appear-

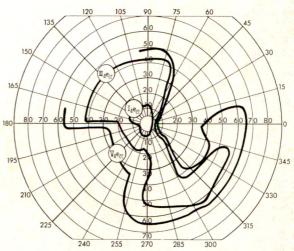
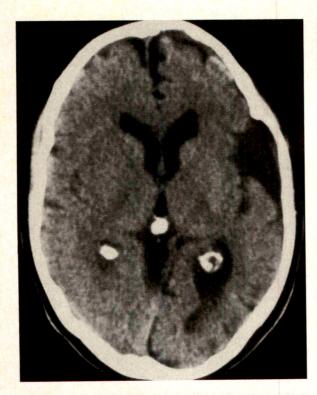


Fig. 2 (Rosenberg and Burde). Kinetic visual field demonstrating relative central scotoma with dense arcuate bundle defects.

ance. There is a spectrum of optic nerve anomalies including optic pit, hypoplastic disk, megalopapilla, morning glory syndrome, optic disk dysplasia, as well as optic nerve coloboma.1,2 Some authors believe that these other optic disk anomalies are of separate origin from coloboma.3,4 However, there are shared features among some of these congenitally anomalous disks that often defy accurate categorization. There are numerous reports documenting the association of any of these optic nerve anomalies with systemic abnormalities frequently involving the central nervous system. 2,4-28 To our knowledge, this is the first report of colobomatous optic nerve occurring in association with an arachnoidal brain cyst. There are several ocular associations that deserve special mention with respect to their clinical significance.

An optic pit is a round, localized depression within the disk substance. It is commonly located at the temporal disk margin. An associated peripapillary chorioretinal pigment disturbance may be present. ²⁹ Visual acuity is usually normal unless a serous macular detachment is present or has caused a persistent maculopathy. ³⁰ The source of serous fluid is not known, although it is thought to originate from either the vitreous, leakage of vessels within the pit or from the choroid, or spinal fluid. Even in the absence of a macular detachment arcuate visual field defects may be detected.

A hypoplastic disk is usually smaller than normal in size. This anomaly may be associated



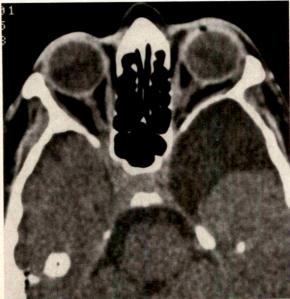


Fig. 3 (Rosenberg and Burde). Computed tomographic scans of the head and orbit. Top, A large, low-density area anterior to the right temporal lobe in the middle cranial fossa is seen. Bottom, Inward bowing of the posterolateral wall of the right orbit is seen. Focal hypoplasia of the right frontal and temporal lobes is evident.

with various endocrinologic abnormalities, especially growth hormone deficiency.

Megalopapilla refers to an optic disk that is larger than normal. Its occurrence is much less

common than hypoplasia. It has been found in association with midline cranial abnormalities.

In morning glory syndrome, the disk is enlarged, pink, and funnel-shaped and contains fibroglial-appearing tissue in its center with a surrounding elevated anulus of chorioretinal pigment disturbance. The origin of the retinal vessels is obscured by the central tissue. The vessels appear narrowed and course radially over the disk margin. Most reported cases have been unilateral, with visual acuity ranging from 20/40 to no light perception. In a recent review, only one reported patient had a visual acuity of 20/20. Optic nerve dysplasia differs from morning glory syndrome only in that the center of the disk is elevated rather than excavated.

Several optic nerve anomalies occur with basal encephalocele, including optic nerve coloboma, 32-34 optic nerve pit, 27 megalopapilla, 2 morning glory syndrome, 34 and optic nerve dysplasia.2 Basal encephalocele should be suspected in a child manifesting an anomalous optic nerve and any midline craniofacial and midfacial anomaly such as cleft lip or palate, hypertelorism, or agenesis of the corpus callosum. The abnormality may first appear as a pulsating mass in the nose, oropharynx, or orbit. Attempted biopsy of the lesion must be avoided and neuroradiologic studies obtained. Basal skull x-rays show a bony defect and computed tomographic scans show protrusion of brain and meningeal tissue in the bony defect.

The difficulty often found in classifying an anomalous optic disk is demonstrated by our patient. Her optic disk exhibited characteristics seen in more than one of the aforementioned congenital optic nerve anomalies. Its large size, funnel shape, and surrounding chorioretinal pigment ring are similar to findings in the morning glory syndrome; however, the disk in our patient lacked the central tuft of fibroglial tissue characteristic of that anomaly. Rather, the origin of the retinal vessels was seen clearly within a deeply excavated nerve head, which is more typical of a colobomatous defect.

As noted previously, it is common for patients with any of the optic nerve anomalies to have subnormal vision. However, progressive visual loss from baseline should arouse suspicion. Our patient had well-documented, progressive visual loss over more than 15 years, and neuroradiologic study confirmed the presence of a space-occupying lesion compressing the optic nerve. This case underlines the importance of obtaining an accurate ocular history. Diminished central visual acuity, abnor-

mal pupillary response, altered visual field, and nerve fiber layer loss should alert the physician to the probability of neuropathic visual loss in any patient with unexplained visual loss.

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Jack Kayes, M.D., referred this patient to us for neuro-ophthalmologic consultation.

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Ophthalmologic and Electro-oculographic Findings in Gardner's Syndrome

Emil A. Stein, M.D., and Kevin D. Brady, M.D.

We examined six patients with Gardner's syndrome, eight first-degree relatives, and 31 age- and sex-matched controls to document the presence, distribution, and morphologic features of congenital hypertrophy of the retinal pigment epithelium. Patients with Gardner's syndrome had multiple, bilateral lesions, with 288 of 346 foci (83%) located posterior to the equator. Linear-shaped congenital hypertrophy of the retinal pigment epithelium, a distinctive finding in these patients, accounted for 44 of 140 large lesions (31%). Despite multifocal fundus involvement, results of electrooculography were normal in all eyes tested.

Congenital hypertrophy of the retinal pigment epithelium occurs either as an isolated finding or in association with such systemic disorders as familial microcephaly, Gardner's syndrome (intestinal polyposis, osteomas, and soft tissue abnormalities), and familial polyposis coli. Lesions are round to oval in shape, with well-defined borders that may be smooth, scalloped, or irregular. They are typically flat and stationary in size, ranging from 0.1 to 14 disk diameters in length. Hypopigmented peripheral margins or depigmented lacunae appear in some of the lesions. In systemic disorders, the lesions are usually multiple and bilateral.

In 1980, Blair and Trempe² first identified congenital hypertrophy of the retinal pigment epithelium in Gardner's syndrome. Lewis and coworkers³ observed bilateral or multiple lesions in every affected member of three kindreds; however, they noted normal fundi in eight patients with Gardner's syndrome from

four other families. Traboulsi and associates⁴ reported that 90.2% of their patients with Gardner's syndrome had pigmented fundus lesions, with 78.1% having bilateral findings. This suggested that bilateral or multiple lesions were specific and sensitive clinical markers of Gardner's syndrome and were related to the widespread expression of an abnormal gene in retinal pigment epithelial cells.

Diffuse expression of an abnormal gene could impair the functional integrity of the retinal pigment epithelium, a condition that electro-oculography may detect. We initiated this study to define the distribution and morphologic features of congenital hypertrophy of the retinal pigment epithelium as well as the electro-oculographic findings in patients with Gardner's syndrome.

Patients and Methods

Patients were recruited for this study through contacts with 39 gastroenterologists in the Denver metropolitan area. Patients with Gardner's syndrome (Group 1) and their firstdegree relatives (Group 2) underwent comprehensive ophthalmologic examinations, including ocular and systemic history reviews, refractions, color vision testing, visual field and motility evaluations, slit-lamp biomicroscopy, and tonometry. Direct and indirect ophthalmoscopy, including scleral depression when possible, and biomicroscopy with a 90diopter lens allowed accurate documentation of lesions in retinal drawings. Fundus photography was performed on all except the youngest patient. Electro-oculography was conducted on all cooperative patients.

A control group (Group 3) from the general eye clinic populations of the University of Colorado Health Sciences Center and The Children's Hospital was carefully evaluated to detect any pigmented lesions in normal eyes. This group consisted of age- and sex-matched pa-

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tients, without severe ocular diseases, who were seen for routine examinations.

Lesions of congenital hypertrophy of the retinal pigment epithelium in the University of Colorado Department of Ophthalmology 35-mm slide files were also reviewed. This reference group (Group 4) consisted of 39 previously examined patients without Gardner's syndrome.

Statistical comparisons were conducted using chi-square analyses.

Results

The mean age of the six patients in Group 1 was 42.7 years (range, 20 to 69 years). Exploratory laparotomy with colon resection preceded the diagnosis of Gardner's syndrome in each of these subjects.

Group 2 consisted of eight patients, with an average age of 18.6 years (range, 6 to 63 years). This included seven offspring and one sibling of patients with Gardner's syndrome. No polyps were detected on barium studies of the upper and lower gastrointestinal tract in three of the offspring. Two of these three patients had soft tissue cyst excisions and large skin nevi. Colonoscopy demonstrated ulcerative colitis in a fourth child. A diagnosis of familial polyposis was made after an exploratory laparotomy in the only Group 2 sibling.

Best-corrected visual acuity was 20/20 or better in each eye of all patients in Group 1 and Group 2, except one uncooperative child in Group 2. Two patients from Group 1 and one from Group 2 had prominent, multiple, bilateral iris nevi. Results of the remainder of the ophthalmologic examinations were normal, except for retinal lesions (Figure). All Group 1 patients had multiple, bilateral foci of congenital hypertrophy of the retinal pigment epithelium. Three Group 2 patients had bilateral lesions, but only one had multiple foci in each fundus. Three Group 2 patients had unilateral congenital hypertrophy of the retinal pigment epithelium, and the last two had no pigmentary abnormalities. Of the 31 patients in Group 3, one had bilateral and one had unilateral congenital hypertrophy of the retinal pigment epithelium.

The lesion locations in each eye in Group 1 were counted and summated by retinal quadrant (Table 1). Of 346 lesions in Group 1 patients, 192 were temporal to the fovea com-

pared to 154 nasal to the fovea (P < .05). No attempt was made to analyze statistically the small number of lesions in patients in Groups 2 and 3.

Lesion locations, in relation to the equator, were similarly evaluated in Group 1 patients (Table 2). Of 346 foci, 288 were posterior to the equator compared to 58 anterior to the equator (P < .005). In five of 12 eyes, there were no abnormalities located anteriorly. Right eyes had 38 foci of congenital hypertrophy of the retinal pigment epithelium anterior to the equator compared to 20 in left eyes (P < .05). Asymmetric quadrantic and hemiretinal distributions of lesions were present in left eyes posterior to the equator. In this subgroup, the superotemporal quadrant (P < .05) and the superior hemiretina (P < .05) were the most frequent locations of lesions.

Morphologic evaluations of congenital hypertrophy of the retinal pigment epithelium in each patient group showed significant asymmetric shape distributions in all Group 1 size categories (P < .005) (Table 3). As the size of lesions in Group 1 increased, the percentage of round shapes decreased and the percentage of oval lesions increased (Table 4). The number of linear-shaped lesions in Group 1 was significantly higher than that in Group 4 (Table 5).

One or more pigmentary variations were observed in 62 lesions in Group 1. There were 31 peripheral hypopigmented zones and 12 depigmented lacunae. Sixteen hypopigmented regions adjoining hyperpigmented foci and nine atrophic foci were seen.

Electro-oculographic studies were conducted on all Group 1 and five Group 2 patients. The average photopic to scotopic ratios were 3.0 (range, 2.3 to 4.0) and 3.6 (range, 2.1 to 5.5) for Groups 1 and 2, respectively. All ratios were within the normal range for our laboratory.

Discussion

The clinical recognition of congenital hypertrophy of the retinal pigment epithelium probably dates back to Mauthner's 1868 report¹² of "atypical pigment development in the retina." In 1911, Höeg¹³ described congenital grouped pigmentation of the retina. Reese and Jones¹⁴ wrote of "benign melanomas of the retinal pigment epithelium" in 1956. Subsequently, Reese¹⁵ used the term "congenital hyperplasia of the pigment epithelium of the retina" when



Figure (Stein and Brady). Congenital hypertrophy of the retinal pigment epithelium. Top left, Oval lesion in a first-degree relative with hypopigmented margin and depigmented lacunae near the margin. Top right, Similar lesion with hyperpigmented foci in a patient with Gardner's syndrome. Middle left, Linear lesion with hypopigmented periphery. Middle right, Linear hypopigmentation containing an array of hyperpigmented foci. Bottom left, Linear lesion in the midperiphery. Bottom right, Linear lesion with adjacent hypopigmented region.

TABLE 1

LOCATIONS OF CONGENITAL HYPERTROPHY OF THE RETINAL PIGMENT EPITHELIUM
IN PATIENTS WITH GARDNER'S SYNDROME (GROUP 1)

		QUADRAM	NTIC DISTRIBUTION	NS			HEMIRETINAL C	ISTRIBUTIONS	
EYES	SUPERO- NASAL	SUPERO- TEMPORAL	INFERO- TEMPORAL	INFERO- NASAL	ALL	SUPERIOR HEMI- RETINA	INFERIOR HEMI- RETINA	NASAL HEMI- RETINA	TEMPORAL HEMI- RETINA
Right	46	48	53	38	185	94	91	84	101
Left	38	55	36	32	161	93	68	70	91
Both	84	103	89	70	346	187	159	154	192

TABLE 2
EQUATORIAL DIVISION OF QUADRANTIC LOCATIONS OF CONGENITAL HYPERTROPHY OF THE RETINAL PIGMENT EPITHELIUM IN PATIENTS WITH GARDNER'S SYNDROME (GROUP 1)

	dr.	ANTERI	OR QUADRANTS			POSTER	RIOR QUADRANTS	3		
EYES	SUPERO- NASAL	SUPERO- TEMPORAL	INFERO- TEMPORAL	INFERO- NASAL	ALL	SUPERO- NASAL	SUPERO- TEMPORAL	INFERO- TEMPORAL	INFERO- NASAL	ALL
Right	8	11	11	8	38	38	37	42	30	147
Left	2	6	6	6	20	36	49	30	26	141
Both	10	17	17	14	58	74	86	72	56	288

TABLE 3
MORPHOLOGIC CHARACTERISTICS OF CONGENITAL HYPERTROPHY OF THE RETINAL PIGMENT EPITHELIUM

	1				DISTRIBUTION	ONS OF L	ESIONS BY SIZE	AND SHAP	E			
PATIENT		<	<150 μM			15	0–500 μм				>500 µм	1.000
GROUP	ROUND	OVAL	IRREGULAR	LINEAR	ROUND	OVAL	IRREGULAR	LINEAR	ROUND	OVAL	IRREGULAR	LINEAR
Group 1	181	25	0	0	27	20	10	26	10	24	5	18
Group 2	10	1	0	0	3	6	0	0	2	0	0	0
Group 3	3	0	0	0	1	0	0	0	0	0	0	0

referring to lesions we now call congenital hypertrophy of the retinal pigment epithelium. The hypertrophy, rather than hyperplasia, of the retinal pigment epithelium in these lesions was demonstrated by Kurz and Zimmerman¹⁶ in 1962. Solitary and grouped lesions have been noted to be similar clinically and histopathologically.^{7,17,18} While we are unaware of any histopathologic study of congenital hypertrophy of the retinal pigment epithelium in a patient with Gardner's syndrome, recent reports have implied similarity to findings in non-Gardner's syndrome patients.²⁻⁴

The present study documented the predominant posterior and temporal locations of congenital hypertrophy of the retinal pigment epithelium in Gardner's syndrome. This temporal predominance is consistent with the observations of Purcell and Shields⁸ in non-Gardner's syndrome patients. We found that one eighth of all lesions, and almost one third of lesions larger than 150 µm, were linear in shape. The number of linear lesions in patients with Gardner's syndrome was significantly higher than that in the reference group (Group 4).

The electro-oculographic findings are depen-

TABLE 4
SHAPE DISTRIBUTIONS OF CONGENITAL
HYPERTROPHY OF THE RETINAL PIGMENT
EPITHELIUM IN PATIENTS WITH GARDNER'S
SYNDROME (GROUP 1)

LESION	PERCENTAGE	S OF LESIONS BY SIZE	CATEGORIES
SHAPES	<150 μм	150–500 μΜ	>500 µM
Round	87.9	32.5	17.5
Oval	12.1	24.1	42.1
Irregular	0.0	12.0	8.8
Linear	0.0	31.3	31.6

dent on the functional integrity of the retinal pigment epithelium. 11 Buettner demonstrated normal results on electro-oculography in ten patients with solitary lesions of congenital hypertrophy of the retinal pigment epithelium. This was not surprising, since the test measures a mass response and not focal abnormalities of the retinal pigment epithelium. 19,20 Blair and Trempe described one patient with Gardner's syndrome in whom results of electro-oculography were normal. We recorded normal results on electro-oculography in all patients with Gardner's syndrome and first-degree relatives tested.

The cause of congenital hypertrophy of the retinal pigment epithelium is unknown. Traboulsi and associates4 suggested that the widespread expression of an abnormal gene in retinal pigment epithelial cells was the cause of congenital hypertrophy of the retinal pigment epithelium. Previous theories have not focused on a genetic origin. Mann²¹ proposed an aberrant differentiation of cells in the inner layer of the optic cup, the sensory retina, as the cause of the observed pigmentary changes. Hogan and Zimmerman²² suggested that retinal pigment epithelial proliferation in foci of rod and cone agenesis was the cause. Buettner⁷ contradicted these theories and advocated that an abnormal differentiation of a localized patch of retinal pigment epithelial cells was responsible. We observed multifocal retinal lesions; however, electro-oculography did not suggest a diffuse abnormality in the retinal pigment epithelium.

In this study, three first-degree relatives, all 10 years of age or younger, had congenital hypertrophy of the retinal pigment epithelium. Two of these patients had bilateral lesions, indicating a near certainty of Gardner's syndrome. Colonoscopic and radiologic examina-

TABLE 5

COMPARISON OF DISTRIBUTION OF CONGENITAL
HYPERTROPHY OF THE RETINAL PIGMENT
EPITHELIUM IN GROUP 1 AND GROUP 4

		SIZES	AND SHAPE	AND SHAPES OF LESIONS				
	<150 µ	<150 μΜ		μМ	ALL LESIONS			
	NONLINEAR	LINEAR	NONLINEAR	LINEAR	NONLINEAR	LINEAF		
Group 1	206	0	96	44	302	44		
Group 4	267	1	48	3	315	4		
P value*	NS		P <.0	P <.005		P <.005		

*NS, not significant.

tions were postponed because of the low likelihood of surgical intervention at this time. These individuals will be followed up closely.

Traboulsi and associates⁴ found bilateral congenital hypertrophy of the retinal pigment epithelium in two of 42 controls and 32 of 41 patients with Gardner's syndrome. Our study found similar lesions in one of 31 normal subjects and six of six patients with Gardner's syndrome. This differential in the frequency of congenital hypertrophy of the retinal pigment epithelium supports its use in the diagnosis of Gardner's syndrome.

Recent reports, however, of congenital hypertrophy of the retinal pigment epithelium in patients with familial polyposis imply that it may not be as specific a finding for Gardner's syndrome as has been proposed. Li and colleagues diagnosed polyposis coli in two patients after ocular examinations had demonstrated retinal pigment epithelial lesions. As larger groups of patients with polyposis syndromes are examined, congenital hypertrophy of the retinal pigment epithelium may be increasingly noted in association with such syndromes.

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OPHTHALMIC MINIATURE

Who formed the curious texture of the eye, And cloath'd it with the various tunicles, And texture exquisite; with chrystal juice Supply'd it, to transmit the rays of light?

Henry Needler, "A Poem to Prove the Certainty of a God," 1759

Enhancement of the Ocular Hypotensive Effect of Acetazolamide by Diflunisal

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We studied the effect of diflunisal on intraocular pressure in patients with glaucoma who were receiving maximally tolerated therapy. Diflunisal therapy, 500 mg twice daily, was started in 48 patients for one week. No changes were made in their regular antiglaucoma medications. Intraocular pressure was reduced an additional 3.8 ± 3.1 mm Hg (± S.D.) in the acetazolamide-treated patients (P < .0001) and 1.6 ± 1.5 mm Hg in methazolamide-treated patients (P < .02), while no significant reduction in intraocular pressure was found in patients receiving topical medications alone. In 15 acetazolamide-treated patients, total plasma concentrations of acetazolamide after diflunisal therapy were significantly higher than the prediflunisal levels, suggesting a modest decrease in renal excretion. In seven acetazolamide-treated patients, free plasma concentrations of acetazolamide were found to increase 5.6-fold after diflunisal therapy. We concluded that diflunisal potentiated the ocular hypotensive effect of acetazolamide by increasing its free plasma level.

DIFLUNISAL, a noncorticosteroidal drug with analgesic, anti-inflammatory, and antipyretic properties, is used in the treatment of mild to moderate pain, osteoarthritis, or rheumatoid arthritis. ^{1,2} Its inhibitory action on cyclooxygenase metabolism is well established, ¹⁻⁴ yet no ocular effects have been reported. We recently noted an unexpected intraocular pres-

sure reduction in a few acetazolamide-treated glaucoma patients after additional treatment with 500 mg of oral diflunisal twice daily. This led us to consider a possible ocular hypotensive effect of this drug.

We conducted a clinical trial to determine whether or not administration of diflunisal to glaucoma patients receiving maximally tolerated glaucoma therapies would result in a further decrease in intraocular pressure. Additionally, because diflunisal has exceptionally high binding to plasma albumin (99.8% at a concentration of 50 µg/ml), and consequently can unbind partially such compounds as salicylic acid and phenprocoumon, we studied the effect of diflunisal on the plasma binding of acetazolamide in humans.

Material and Methods

This study was reviewed and approved by the Committee on Human Rights in Research. All subjects participated voluntarily and informed consent was obtained from each before enrollment. Of the 48 glaucoma patients, there were 19 men and 29 women, whose mean ± S.D. age was 67.0 ± 12.8 years. Thirty-six patients had open-angle glaucoma, seven had narrow-angle glaucoma, four had secondary glaucoma, and one had congenital glaucoma. All patients were receiving maximally tolerated antiglaucoma medications. Patients were assigned consecutively to the study. Medical regimen included acetazolamide in 28 patients and methazolamide in five patients. All eyes were treated with at least one preparation of topical antiglaucoma medication: pilocarpine (60 eyes); epinephrine or dipivefrin hydrochloride (27 eyes); timolol, levobunolol, or betaxolol (80 eyes); and echothiophate iodide (17 eyes). Upon entering the study, each patient received a full ophthalmologic examination, including determination of visual acuity, slit-lamp exami-

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nation, intraocular pressure measurement (baseline) by Goldmann applanation tonometry, gonioscopy, and ophthalmoscopy with a dilated pupil. Patients were instructed to take oral diflunisal, 500 mg, twice daily for one week, with no change in their regular antiglaucoma medications. One week later, patients returned for determination of visual acuity, slit-lamp examination, intraocular pressure measurement, and a history of side effects. Baseline and follow-up intraocular pressure was measured by the same investigator using the same tonometer at approximately the same time of day.

Eight normal healthy volunteers (four men and four women, aged 52.3 ± 16.4 years) receiving no medications participated in this study as a control group to study the ocular hypotensive effect of diflunisal itself. They were also given 500 mg of oral diflunisal twice daily for one week. Baseline and follow-up examinations were performed in these patients as described above.

In 15 acetazolamide-treated patients, 2 to 3 ml of venous blood was drawn using a vacuum blood sampler containing heparin before and, at the same time of day, after one week of diflunisal therapy for determination of total plasma concentrations of acetazolamide. The blood sample was centrifuged at 5,000 rpm for five minutes, and the plasma was separated and refrigerated until analysis. The plasma of seven of these 15 patients was also subjected to dialysis for determination of acetazolamide's binding to albumin.

Two blood samples were also taken at a oneweek interval from six acetazolamide-treated patients not included in the study. These samples were analyzed for total acetazolamide concentrations.

An in vitro study was performed for the effect of graded concentrations of diflunisal on the plasma binding of acetazolamide. Both drugs were added to the plasma of a single nonglaucomatous individual and duplicate dialyses were performed.

Acetazolamide levels were analyzed by assay against carbonic anhydrase. To determine free acetazolamide levels, dialysis was carried out in a specially constructed cell consisting of two chambers of 1-ml capacity separated by a membrane. After analysis for total drug, 1 ml of plasma was introduced into one compartment and 1 ml of physiologic saline into the other. The solutions were each mixed for 18 hours at 25 C and then analyzed for free and total drug levels.

Results

The addition of diflunisal treatment in acetazolamide-treated patients resulted in intraocular pressure levels that were significantly lower than baseline (Table 1), with a mean \pm S.D. reduction of 3.8 \pm 3.1 mm Hg. Methazolamide-treated patients showed a small but significant decrease in intraocular pressure of 1.6 \pm 1.5 mm Hg. Patients receiving topical medications alone and normal controls showed no significant change in intraocular pressure after diflunisal therapy. There was no relationship between the daily dosage of acetazolamide and intraocular pressure reduction (Figure).

The total acetazolamide plasma levels in 15 patients receiving diflunisal therapy were significantly higher than baseline levels (31.8 \pm 16.1 μ M and 19.1 \pm 9.1 μ M, respectively, P < .015, paired t-test). Plasma unbound acetazolamide concentrations in seven patients increased from 4.3% \pm 2.7% to 16.2% \pm 8.7% after diflunisal therapy. These effects resulted in an increase of free plasma acetazolamide from 1.0 \pm 0.6 μ M to 5.6 \pm 4.1 μ M. In a comparable group of six acetazolamide-treated patients without additional diflunisal treatment, total acetazolamide plasma levels showed no significant change after one week (P > .05, paired t-test).

Increased concentrations of diffunisal caused decreased plasma protein binding of acetazolamide in vitro (Table 2).

TABLE 1
CHANGES IN INTRAOCULAR PRESSURE AFTER
ONE WEEK OF TREATMENT WITH DIFLUNISAL
(MEAN ± S.D.)

	NO. OF		AR PRESSURE (Hg)	
DRUG	EYES	BASELINE	CHANGE	P VALUE*
Acetazolamide [†]	55	18.3 ± 6.1	-3.8 ± 3.1	<.0001
Methazolamide [‡]	10	17.6 ± 2.1	-1.6 ± 1.5	<.02
Topical drugs alone	30	18.8 ± 4.0	-0.7 ± 2.1	NS
Control	16	15.6 ± 3.7	0.0 ± 1.0	NS

^{*}Probability for difference between before and after diffunisal treatment, based on paired *t*-test; NS, not significant.

[†]Treatment included acetazolamide in various doses in addition to topical glaucoma medications.

¹Treatment included methazolamide in various doses in addition to topical glaucoma medications.

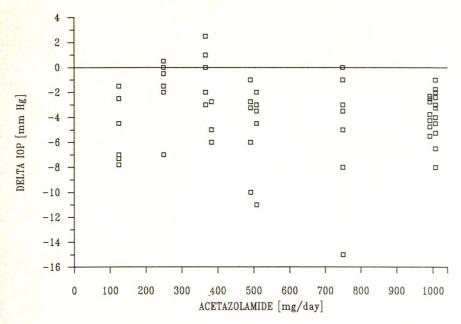


Figure (Yablonski and associates). Reduction in intraocular pressure (IOP) plotted against daily dosage of acetazolamide in acetazolamide-treated patients after one week of diflunisal treatment (n = 55 eyes). No relationship was found between the magnitude of pressure reduction and the dosage of acetazolamide.

Side effects, which were found primarily in the acetazolamide-treated group, included gastrointestinal symptoms (eight patients), fatigue (seven patients), nausea (one patient), paresthesia (one patient), and confusion (one patient). All side effects were mild and well tolerated. Two additional patients receiving acetazolamide were dropped from the study because of severe nausea and extreme confusion; they discontinued diflunisal before the one-week follow-up examination. Among the five patients receiving methazolamide, side effects included mild gastrointestinal symptoms and nausea in one patient each. Two patients receiving topical medications alone showed mild gastrointestinal symptoms after diflunisal.

Discussion

Diflunisal is well absorbed from the intestines and reaches peak plasma levels within two to three hours; steady-state plasma levels are reached within three to nine days on a regimen of 500 mg twice daily. 1-4 Plasma diflunisal is 99.8% protein bound, 5 and it is excreted mostly in the urine as a glucuronide. 1 Diflunisal is generally better tolerated than acetylsalicylate, and its most frequent adverse reactions are nausea, gastrointestinal discomfort, and diarrhea. 1

Our study of glaucoma patients demonstrat-

ed that diflunisal yielded a significant decrease in intraocular pressure in acetazolamide-treated patients with a lesser magnitude of intraocular pressure reduction in methazolamide-treated patients. In acetazolamide-treated patients, the addition of diflunisal was associated with a nearly 50% increase in total plasma levels and a 5.6-fold increase in free plasma levels of acetazolamide.

We also found that diflunisal competed with acetazolamide for binding sites on plasma albumin. The two higher concentrations of diflunisal (Table 2) are roughly equivalent to the plasma concentrations following the dosage of 500 mg twice daily.^{2,3} These in vitro results closely paralleled those seen in vivo in glaucoma patients. Diflunisal has been shown to displace such compounds as salicylate and phenprocoumon,⁵ warfarin,⁷ and oxazepam⁸

TABLE 2
IN VITRO PLASMA BINDING OF 90 μM ACETAZOLAMIDE
IN A SINGLE HUMAN WITH GRADED
CONCENTRATIONS OF DIFLUNISAL

DIFLUNISAL (μм)	UNBOUND ACETAZOLAMIDE (%)
0	7
200	14
400	22
600	26

from human plasma protein. The magnitude of the change induced by diflunisal was greater with acetazolamide than with any of these four compounds.

In this study, the unbound plasma concentrations of acetazolamide increased from 1.0 to 5.6 µM, which apparently caused an additional decrease in intraocular pressure. It is not certain whether or not these concentrations are near the top of the dose-response curve. The full dose-response curve for acetazolamide has not been determined in chronic studies in humans. It may be significant that this free concentration of acetazolamide (5.6 µM) is in the same range as that found for the steep part of the dose-response curve in rabbits for free methazolamide,9 which has the same activity against carbonic anhydrase as acetazolamide. Furthermore, the potentiating effect of diflunisal on intraocular pressure was independent of the total dose of acetazolamide (Figure), which indicated that we were still on the steep part of the dose-response curve for acetazolamide.

A second effect of the combination of diflunisal and acetazolamide was to raise total plasma concentrations of the latter compound; this is in accord with the acidic nature of both compounds and that they are both secreted by the kidney.4,10 Pharmacokinetic studies11 have shown that the plasma protein binding and renal clearance of acetazolamide were significantly reduced by salicylate, which appeared to competitively inhibit the plasma protein binding of acetazolamide and simultaneously to inhibit acetazolamide renal tubular secretion. Diflunisal, like salicylate, probably potentiated acetazolamide's ocular hypotensive effect as a result of the reduction in acetazolamide renal clearance by competitive inhibition in addition to its effect on protein binding of acetazol-

Diflunisal affected the hypotensive action of methazolamide to a lesser degree in comparison with acetazolamide. While acetazolamide is 95% bound to plasma protein, 12 methazolamide is only 55% bound⁹; therefore, unbinding, if it occurs, could not be of as great a magnitude. Furthermore, acetazolamide is excreted 100% unchanged in urine, but only 25% of methazolamide is excreted unchanged in urine. Thus, interference of diflunisal with methazolamide excretion by the kidney could occur to a lesser extent than with acetazolamide.

Systemic acidosis is known to contribute in part to the intraocular pressure lowering effect

of acetazolamide.¹³ The diflunisal-acetazolamide combination may have caused increased acidosis. Blood pH levels were not determined in the present study, and this possibility requires further clarification.

Increased free plasma levels of acetazolamide should cause a higher incidence of side effects as well as an increased ocular hypotensive effect. However, it is not clear whether or not diflunisal potentiates acetazolamide's side effects to the same degree as the ocular hypotensive effects. Two of 30 patients receiving acetazolamide developed side effects severe enough to cause them to be dropped from the study after the addition of diflunisal. No conclusion can be made on the basis of this study, however, since our main purpose was to evaluate the hypotensive effect caused by the addition of diflunisal to acetazolamide and not a comprehensive evaluation of side effects. Future studies are needed to determine if the effect of diflunisal on acetazolamide is merely the equivalent of increasing the dose of acetazolamide or if its enhancement of acetazolamide's intraocular pressure lowering effect is greater than its enhancement of acetazolamide's side effects. Furthermore, the relationship between the acetazolamide dosage, plasma levels of total and free acetazolamide, blood pH levels, plasma diflunisal levels, intraocular pressure, and side effects requires additional study.

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OPHTHALMIC MINIATURE

Correct my view
That the far mountain is much diminished,
That the fovea is prime composer,
That the lid's closure frees me.

Let me be touched
By the alien hands of love forever,
That this eye not be folly's loophole
But giver of due regard.

Richard Wilbur, "The Eye, II," New and Collected Poems New York, Harcourt Brace Jovanovich, 1988, p. 57

Bilateral Superior Oblique Muscle Palsy Associated With Apert's Syndrome

Zane F. Pollard, M.D.

Eleven children had Apert's syndrome and bilateral superior oblique muscle palsy. Of seven patients who underwent surgical exploration of the superior oblique muscle area, five had no superior oblique tendon in either eye and two had only a small fibrous band as a remnant in each eye. All 11 patients had a significant horizontal deviation in primary gaze and downgaze, in addition to a vertical imbalance. The findings led to the conclusion that all patients with craniofacial anomalies, especially those with Apert's syndrome, should be examined for the presence of vertical muscle palsies and particularly bilateral superior oblique muscle palsy.

THE ABSENCE OR PALSY of a rectus muscle has been reported before in craniofacial anomalies. Congenital absence of the superior oblique muscle is rare, whereas the absence of the inferior or superior rectus muscle has been reported much more frequently in patients with craniofacial dysostosis. I examined 11 children, all of whom had bilateral superior oblique muscle palsy associated with Apert's syndrome.

Apert's syndrome was first described by Apert in 1906.¹ It has also been called acrocephalosyndactyly, referring to the combination of a conical-shaped head and fusion of the toes or fingers. All of the patients described herein had craniosynostosis with syndactyly of the toes and fingers. Apert's syndrome involves irregular craniosynostosis, especially of the coronal suture. Alternatively, Crouzon's syndrome involves craniosynostosis, especially of the coronal, lambdoid, and sagittal sutures. The main distinguishing feature between the two syndromes is the presence of syndactyly of

the fingers and toes in Apert's syndrome. Hypoplasia of the maxilla is prominent in Crouzon's syndrome but can also occur in Apert's syndrome. Carpenter's syndrome is an advanced form of Apert's syndrome in which hypogenitalism is prominent. Also seen in Apert's syndrome are optic atrophy, cataracts, strabismus, iris and choroidal colobomas, megalocornea, keratoconus, medullated nerve fibers, pyloric stenosis, pulmonic stenosis, ventricular septal defect, polycystic kidney, hydronephrosis, mental retardation, and hydrocephalus (Table). Most cases of the syndrome represent a fresh mutation, with an autosomal dominant inheritance pattern becoming important after the mutation.

Five of the patients in this study had no superior oblique tendon and two patients had rudimentary superior oblique muscles in each eye.

Case Reports

Case 1

On examination, a 17-year-old boy with Apert's syndrome had 30 prism diopters of

TABLE
CLINICAL CHARACTERISTICS OF PATIENTS WITH
APERT'S SYNDROME

CLINICAL FINDINGS	NO. OF PATIENTS (N=11)
V-pattern esotropia	11
Overacting inferior oblique muscles	8
Underacting superior oblique muscles	11
No superior oblique tendon	5
Fibrous band remnant of	
superior oblique muscles	2
Esotropia in primary position	11
Cataract	1
Coloboma of iris	1
Hydrocephalus	5
Family history of Apert's syndrome	1

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esotropia in primary position, with 45 prism diopters in downgaze and 2 prism diopters in upgaze. Thirty prism diopters of esotropia were present in the primary positon at near and in side gazes. There was 2 prism diopters of left hypertropia in primary position at distance and near, with 16 prism diopters of left hypertropia in right gaze and 10 prism diopters of right hypertropia in left gaze (Figure). There were 14 prism diopters of left hypertropia on left head tilt, with 30 prism diopters of esotropia, and 10 prism diopters of right hypertropia on right head tilt, with 30 prism diopters of esotropia. There was marked underaction of the superior oblique muscle in each eye. The patient had undergone three previous operations on his hands and feet for syndactyly. At surgery, extensive exploration of the superior aspect of each globe failed to show any remnant of the superior oblique tendon. The patient was treated with a 4-mm recession of the medial rectus muscle in each eye, with lowering of one-half tendon width. Each inferior oblique muscle was recessed 10 mm and the right inferior rectus muscle was recessed 4 mm. Six months after surgery, a small esotropia of 4 prism

diopters in primary position at distance and near, with 2 prism diopters of left hypertropia, and 10 prism diopters of esotropia in downgaze were present.

Case 2

A 9-year-old girl with Apert's syndrome was examined after two operations each for syndactyly and craniostenosis. Examination showed 30 prism diopters of esotropia in primary position at distance and near, with 10 prism diopters in upgaze, 45 prism diopters in downgaze, and 30 prism diopters to each side. Six prism diopters of right hypertropia was present in primary position at distance and near, with 10 prism diopters of right hypertropia on left gaze and 6 prism diopters of left hypertropia on right gaze. Marked underaction of each superior oblique muscle was present, with 25 prism diopters of right hypertropia down to the left and 25 prism diopters of left hypertropia down to the right. At surgery, only a 4-mm-wide fibrous remnant was present for each superior oblique tendon. Each remnant was tucked 18 mm and each medial rectus muscle was recessed 4.5 mm and lowered 5 mm. One year



Figure (Pollard). Case 1. A-pattern esotropia with absent superior oblique muscles associated with Apert's syndrome.

postoperatively, 4 prism diopters of right hypertropia was present in primary position at distance and near, with ortho horizontally in primary position and 10 prism diopters of esotropia in downgaze.

Case 3

This 5-year-old boy with Apert's syndrome had two previous operations for craniostenosis, with the placement of one shunt for hydrocephalus. He had marked syndactyly of both hands and feet. Examination showed 25 prism diopters of esotropia in primary position at distance and near, with ortho in upgaze and 45 prism diopters of esotropia in downgaze. There was no hypertropia in primary position, but there was 14 prism diopters of right hypertropia on left gaze and 14 prism diopters of left hypertropia on right gaze, with marked overaction of each inferior oblique muscle and marked underaction of each superior oblique muscle. At surgery, each inferior oblique muscle was recessed 10 mm and each medial rectus muscle was recessed 4 mm and lowered 5 mm. Extensive exploration of the superior aspect of each globe failed to disclose the superior oblique tendon. Six months postoperatively, the patient was ortho in primary position and had 10 prism diopters of esotropia in downgaze, with 4 prism diopters of right hypertropia on left gaze and 4 prism diopters of left hypertropia on right gaze.

Case 4

This 16-year-old boy had two shunts for hydrocephalus and had undergone two operations for syndactyly of the hands. Examination showed a large V-pattern esotropia and marked underaction of each superior oblique muscle measuring 35 prism diopters of esotropia in primary position at distance and near, with 10 prism diopters in upgaze and 60 prism diopters in downgaze, and 4 prism diopters of right hypertropia in primary position at distance and near. There was 12 prism diopters of right hypertropia on left gaze and 8 prism diopters of left hypertropia on right gaze. There were also 10 prism diopters of right hypertropia on right head tilt and 8 prism diopters of left hypertropia on left head tilt, with 35 prism diopters of esotropia on head tilt to each side. Overaction of the inferior oblique muscle was noted in each eye. At surgery, a 10-mm recession of each inferior oblique muscle was combined with a 5-mm recession and 10-mm lowering of

the medial rectus muscle in each eye. Extensive exploration of the superior aspect of each globe failed to disclose any superior oblique tendon. Postoperatively, 15 prism diopters of esotropia remained in downgaze, with ortho in primary position horizontally and 2 prism diopters of right hypertropia in primary position at distance and near.

Cases 5 and 6

These two children with Apert's syndrome both had a large V-pattern esotropia and marked underaction of each superior oblique muscle. At surgery, no superior oblique tendon was seen after extensive exploration of the superior aspect of each globe. Postoperatively, a significant esotropia remained in downgaze.

Case 7

This 13-year-old girl with Apert's syndrome had a large V-pattern esotropia and left hypertropia in primary position, with underaction of each superior oblique muscle and a left hypertropia on right gaze and left head tilt, and a right hypertropia on left gaze and right head tilt. Exploration of the superior aspect of each globe showed a small fibrous inelastic superior oblique tendon, which was tucked 14 mm in each eye. Recession of each medial rectus muscle and lowering of each medial rectus muscle and lowering of each medial rectus muscle 5 mm was also performed. Postoperatively, only a small residual esotropia in downgaze remained, but there was no effect from the tuck on each superior oblique tendon.

Cases 8, 9, 10, and 11

Each of these patients with Apert's syndrome had craniostenosis and syndactyly of the hands and feet. Each also had a large V-pattern esotropia, with marked underaction of each superior oblique muscle and marked overaction of each inferior oblique muscle. A small hypertropia was present in primary position at distance and near, with a right hypertropia on left gaze and right head tilt and a left hypertropia on right gaze and left head tilt. Each patient underwent a 10-mm recession of each inferior oblique muscle and a 5-mm recession of each medial rectus muscle with lowering of each medial rectus muscle 5 mm. The area of the superior oblique muscle was not explored in these patients, but each had the clinical findings of a V-pattern esotropia with bilateral superior oblique muscle palsy.

Discussion

Congenital absence of an extraocular muscle, although rare, involves most commonly the inferior rectus muscle.2 Diamond and associates³ described five cases of craniostenosis in which the superior rectus muscle was absent in each eye in two patients. One had an absent right inferior rectus muscle and the other had an absent left superior oblique, left superior rectus, and right superior oblique muscle. A third patient had an absent inferior oblique muscle bilaterally. Pinchoff and Sandall4 described one patient with Apert's syndrome who had no superior oblique muscle in either eye and one patient with Crouzon's syndrome who had an absent right superior oblique muscle. Helveston, Giangiacomo, and Ellis⁵ described five patients with unilateral absence and one patient with bilateral absence of the superior oblique muscle. Four of their patients had a significant horizontal strabismus, which was considered suggestive of the absence of the superior oblique muscle. Each of our patients also had a significant esotropia. The presence of craniofacial anomalies was not discussed in their study. Barnes and Boniuk⁶ reported a case of anencephaly with bilateral absence of the superior oblique muscle as seen at autopsy. Absence of the superior rectus muscle in Apert's syndrome is well recognized. 7,8 However, an extensive review of 270 cases of superior oblique muscle paralysis by von Noorden, Murray, and Wong9 did not mention any cases of craniofacial anomalies. Additionally, a report of 20 cases of congenital superior oblique muscle palsy by Reynolds, Biglan, and Hiles¹⁰ did not mention any cases of Apert's or Crouzon's syndrome.

All of the children in this study underwent computed tomography as part of the evaluation of their craniofacial status before ophthalmologic evaluation. Although the scans involved the orbits as well as the cranium, no particular attention was paid to the extraocular muscles. In the future, our patients with Apert's syn-

drome will undergo computed tomography of the cranium and the extraocular muscles at the same time. While many of these children will not have an absence of the superior oblique muscle, many will still have a bilateral superior oblique muscle palsy. I agree with Helveston, Giangiacomo, and Ellis⁵ that in the presence of a significant horizontal deviation in association with bilateral superior oblique palsy, one should consider the absence of this muscle. This is particularly so in the presence of Apert's syndrome.

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Vertical Abnormal Retinal Correspondence in Three Patients With Congenital Absence of the Superior Oblique Muscle

Toshihiko Matsuo, M.D., Hiroshi Ohtsuki, M.D., Yuka Sogabe, M.D., Haruhito Konishi, M.D., Kayoko Takenawa, C.O., and Yoshimasa Watanabe, M.D.

Three patients with large vertical deviations diagnosed as palsy of the superior oblique muscle were found to have a congenital absence of the muscle during surgery. They also showed large, vertical abnormal retinal correspondence, which caused paradoxical vertical diplopia when the deviations were corrected with Fresnel membrane prisms or surgery. Each patient showed large, long-standing, vertical deviations for which head tilting could not have compensated.

CONGENITAL PALSY of the superior oblique muscle is a common cause of vertical deviation of the eyes. Surgical intervention sometimes demonstrates hypoplastic muscle fibers of the superior oblique muscle, but the complete absence of the muscle is rare. ¹⁻⁷ Its absence was also reported to be associated with craniofacial dysostosis (Crouzon's disease)⁸ and Down's syndrome. ⁹

Abnormal retinal correspondence is a sensory adaptation in strabismus in which there is retinal correspondence between the fovea in the fixating eye and a peripheral retinal point in the nonfixating eye. Abnormal retinal correspondence described so far has shown horizontal spans and has been mainly associated with esotropia and exotropia. Small vertical abnormal retinal correspondence has been associated with horizontal abnormal retinal correspondence in amblyopic eyes, but apparent, large abnormal retinal correspondence is considered rare. ^{10,11}

We examined three patients with a diagnosis of superior oblique muscle palsy who showed large, long-standing vertical deviations. Surgical intervention demonstrated the absence of the muscle in each patient, which prompted us to weaken the antagonist inferior oblique muscle or recess the ipsilateral superior rectus muscle, or both. The vertical abnormal retinal correspondence led to paradoxical vertical diplopia when the ocular deviations were corrected preoperatively with Fresnel membrane prisms and also postoperatively, after surgical realignment of the eyes.

Case Reports

Case 1

A 12-year-old girl was referred to us with the diagnosis of right superior oblique muscle palsy. The mother noticed squinting at 3 years of age. On admission, June 13, 1983, bestcorrected visual acuity was R.E.: 20/15 and L.E.: 20/20. Results of examinations of the anterior segments and fundi were unremarkable. She had a left head tilt of about 5 degrees. Synoptophore examination demonstrated an objective deviation of 10 prism diopters of exotropia and 28 prism diopters of right hypertropia, and subjective deviation of 10 prism diopters of exotropia and 14 prism diopters of right hypertropia. A right superior oblique muscle palsy was confirmed with a positive Bielschowsky test (Fig. 1). She showed alternate foveal fixation, with right eye preference. A vertical abnormal retinal correspondence was demonstrated by the positive and negative afterimage test and the afterimage transfer test. Bagolini's striated glasses test showed alternating suppression without correction and vertical diplopia at near and distance using a Fresnel prism with 25 prism

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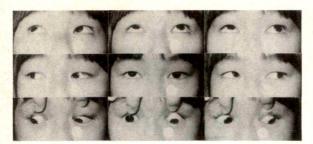


Fig. 1 (Matsuo and associates). Case 1. Preoperative nine cardinal eye positions showing right superior oblique muscle palsy.

diopters base down over the right eye. A dark red glass over the right eye with prism neutralization showed vertical diplopia of 14 prism diopters. No stereopsis was demonstrated.

At surgery the right inferior oblique muscle was recessed 10 mm when the right superior oblique muscle was found to be absent (Fig. 2). With the left eye fixed at distance there were 20 prism diopters of right hypertropia in primary position, 40 prism diopters with right head tilt, and 14 prism diopters with left head tilt. Bagolini's striated glasses test showed vertical diplopia in primary position, alternating suppression in right head tilt, and fusion in left head tilt. Prism neutralization with 10 prism diopters base down in the right eye and 10 prism diopters base up in the left resulted in vertical diplopia of 14 prism diopters with a dark red glass.

On July 8, a 4-mm recession of the right superior rectus muscle was performed. The postoperative deviation with the left eye fixed at distance was 10 prism diopters of right hypertropia in primary position, 18 prism diopters in right head tilt, and 2 prism diopters in left head tilt. Bagolini's striated glasses test showed anomalous fusion in the primary position, alternating suppression in right head tilt, and vertical diplopia in left head tilt. Prism neutralization with 10 prism diopters base down in the right eye resulted in vertical diplopia of 14 prism diopters with a red glass.

Case 2

A 4-year-old boy was referred to us with a diagnosis of right superior oblique muscle palsy. He had shown head tilt to the left, with hypertropia in the right eye, from 1 year of age. On admission, April 30, 1987, best-corrected visual acuity was 20/20 in each eye, with cycloplegic refractive errors of +1.0 diopter in each eye. He showed head tilt to the left of about 10

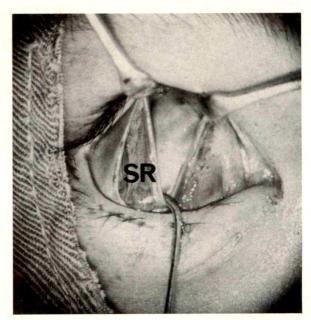
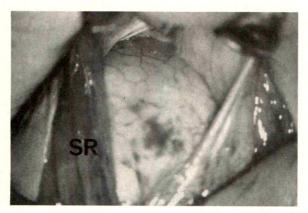


Fig. 2 (Matsuo and associates). Case 1. Intraoperative photograph nasal to the superior rectus muscle (SR) showing absence of right superior oblique muscle.

degrees. The deviation at distance with the left eye fixed in primary position was 20 prism diopters of esotropia and 20 prism diopters of right hypertropia. He showed a V-pattern esotropia and a positive Bielschowsky test. The fixation pattern of each eye was foveal. He showed alternating fixation, with fixation preference to the left eye. The results of afterimage test, Bagolini's striated glasses test, and the red glass test were uncertain because of his age. Stereopsis was not detected.

On July 6, scheduled 14-mm plication of the right superior oblique muscle was replaced by 5-mm recession of the right superior rectus muscle and recession of the right inferior oblique muscle by Parks' method, as the right superior oblique muscle was absent (Fig. 3). The postoperative deviations at distance with the left eye fixed were 20 to 25 prism diopters of left hypertropia in primary position, 16 to 18 prism diopters of left hypertropia in left gaze, and 20 to 25 prism diopters of left hypertropia in right gaze. Ocular motility showed underaction of the right superior rectus muscle. Therefore, on July 20, the recessed superior rectus muscle was advanced to its original insertion. The postoperative deviations at distance with the left eye fixed were 10 prism diopters of esotropia and 8 prism diopters of



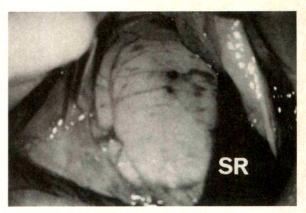


Fig. 3 (Matsuo and associates). Intraoperative photograph nasal (left) and temporal (right) to the superior rectus muscle (SR) showing absence of right superior oblique muscle.

left hypertropia in primary position; 16 prism diopters of esotropia and 12 prism diopters of right hypertropia in right head tilt; and 16 prism diopters of esotropia and 35 prism diopters of left hypertropia in left head tilt. Bagolini's striated glasses test under prism neutralization showed vertical diplopia at near and right suppression at distance. Computed tomography of the orbit showed absence of the right superior oblique muscle (Fig. 4).

Case 3

A 12-year-old boy was referred to us with a diagnosis of right superior oblique muscle palsy. He had developed head tilt to the left at age 5 years. On admission, June 25, 1987, best-corrected visual acuity was R.E.: 20/15 and L.E.: 20/20 with refractive errors of R.E.: -1.25

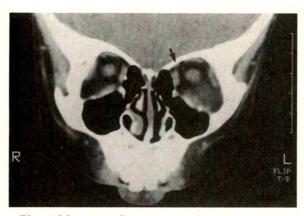


Fig. 4 (Matsuo and associates). Case 2. Computed tomography of the orbit showing absence of right superior oblique muscle in coronal section posterior to the globe. Note left superior oblique muscle (arrow).

diopters and L.E.: -1.5 diopters. Results of ophthalmoscopy and examination of the anterior segments were unremarkable. He showed head tilt to the left of about 5 degrees and face turn to the left of about 5 degrees. The objective angle in primary gaze with the head straight measured with synoptophore was 18 prism diopters of esotropia and 32 prism diopters of right hypertropia, whereas the subjective angle was 20 prism diopters of esotropia and 10 prism diopters of right hypertropia. The deviation in each gaze (Fig. 5) showed a pattern of the right superior oblique muscle palsy. He had a positive Bielschowsky test. The fixation patterns of both eyes were steady foveal. He showed alternate fixation, with right eye preference. The afterimage test showed vertical abnormal retinal correspondence in positive and alternating suppression in negative. Bagolini's striated glasses test showed a left suppression without correction and vertical diplopia using Fresnel membrane prism neutralization, with 30 prism diopters base down in the right eye at near and distance. A dark red glass in the left eye showed vertical diplopia of more than 14 prism

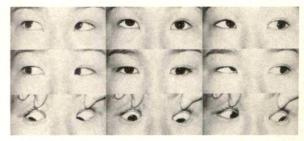
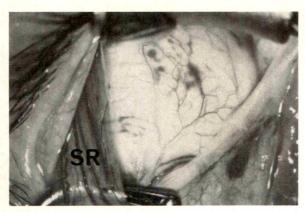


Fig. 5 (Matsuo and associates). Case 3. Preoperative nine cardinal eye positions.



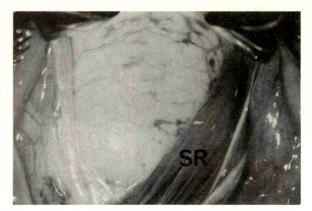


Fig. 6 (Matsuo and associates). Case 3. Intraoperative photograph nasal (left) and temporal (right) to superior rectus muscle (SR) showing absence of right superior oblique muscle.

diopters, with prism neutralization at distance. Stereopsis was not detected.

On Aug. 10, 14-mm plication of the right superior oblique muscle was attempted, but the muscle was completely absent (Fig. 6), and we performed a recession of the right inferior oblique muscle by Parks' method. The postoperative deviation was 15 prism diopters of esotropia and 15 prism diopters of right hypertropia in primary position at distance. Prism neutralization with 15 prism diopters base down in the right eye resulted in vertical diplopia of more than 14 prism diopters. On Aug. 21, 3.5-mm recession of the left inferior rectus muscle and 3.5-mm resection of the left superior rectus muscle were performed. The postoperative deviation was 15 prism diopters of esotropia and 4 prism diopters of right hypertropia in primary position; 4 prism diopters of esotropia and 12 prism diopters of right hypertropia in right head tilt; and 14 prism diopters of esotropia and 12 prism diopters of left hypertropia in left head tilt. He began to wear neutralizing Fresnel prisms with 15 prism diopters base out in the right eye and 4 prism diopters base up in the left eye, which showed vertical diplopia of more than 14 prism diopters and horizontal diplopia of uncrossed 8 prism diopters with Bagolini's striated glasses. Computed tomography of the orbit showed absence of the right superior oblique muscle (Fig. 7).

Discussion

We currently use plication of the superior oblique muscle in cases of congenital superior

oblique muscle palsy, as recommended by de Decker, 12 with good results. This direct surgical approach to the muscle led us to discover the congenital absence of the superior oblique muscle. We had approached the muscle by a fornix incision parallel to the corneoscleral limbus just temporal to the superior rectus muscle and visualized the insertion of the superior oblique muscle by retracting the superior rectus muscle nasally with a muscle hook passed beneath its insertion. In all three cases, we searched for the superior oblique muscle insertion nasally to the superior rectus muscle as well as near to the trochlear portion because the insertion had been reported to be sometimes anomalous. Computed tomography of the orbit in Patients 2 and 3 demonstrated absence of both the trochlea and the superior oblique mus-

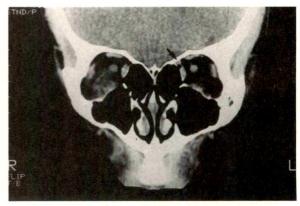


Fig. 7 (Matsuo and associates). Case 3. Computed tomography of the orbit showing absence of right superior oblique muscle in coronal section posterior to the globe. Note left superior oblique muscle (arrow).

cle posterior to the globe. Clinically, these patients showed large vertical deviations with a positive Bielschowsky test, which is typical for patients with congenital superior oblique muscle palsy. These findings indicate that our three patients had a congenital absence of the superior oblique muscle, although it is possible that the muscle had a highly anomalous insertion or that it was extremely hypoplastic. Congenital absence of the superior oblique muscle should be considered in patients with congenital superior oblique muscle palsy with an unusually large vertical deviation. In such patients, an alternative surgical approach such as weakening of the inferior oblique muscle or recession and resection of vertical recti muscles must be substituted for plication of the superior oblique muscle.

Vertical abnormal retinal correspondence was confirmed in our three patients by the following findings: (1) despite foveal fixation they showed vertical abnormal retinal correspondence in afterimage tests (except for Patient 2, who was too young to understand the test), (2) the objective and the subjective angles measured in Patients 1 and 3 showed considerable differences, and (3) preoperative and postoperative prism neutralization of the objective angles with Fresnel membrane prisms resulted in paradoxical vertical diplopia in all cases. There are several possible explanations as to why vertical abnormal retinal correspondence is rarer than horizontal abnormal retinal correspondence: (1) the vertical fusional range is narrower than the horizontal one, (2) vertical deviation is unstable and changes in size according to the direction of gaze and head posture, and (3) there is a presumed anatomic difference in the projection pattern of the nerve fibers between the vertical halves and the horizontal halves of the visual field. Our three patients, because of a common congenital absence of the superior oblique muscle, showed large and long-standing vertical deviations, which they could not have compensated for with head tilting. In contrast, Kaufmann and Kluxen³ described a patient with congenital absence of the superior oblique muscle who showed apparent normal retinal correspondence, as her deviation became hyperphoric with head tilting. These points were thought to contribute the unusual formation of vertical abnormal retinal correspondence in the present

three patients. In our patients, the vertical deviations could have been too large to be compensated for with head tilting and they formed anomalous fusion with vertical abnormal retinal correspondence instead of using suppression. In turn, this formation of vertical abnormal retinal correspondence would have resulted in smaller angles of head tilt than are normally observed in patients with superior oblique muscle palsy.

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EDITORIAL

Predicting the Risk of Hereditary Retinoblastoma

J. L. Wiggs and T. P. Dryja

Retinoblastoma affects approximately one infant in 20,000 live births in the United States each year. Between 60% and 70% of the cases are sporadic and the disease will not be inherited. The remaining 30% to 40% have a predisposition to tumor formation that can be inherited as an autosomal dominant trait and can be termed hereditary retinoblastoma. Of these, one third are the result of inheritance of a retinoblastoma-predisposing mutation from a

carrier parent, and two thirds are tumors caused by new germ line mutations that were not present in the parents but can be transmitted to future offspring.1 Ophthalmologists are often asked to provide genetic counseling for patients of child-bearing age who have had retinoblastoma or who have family members affected with the tumor. Parents of an affected child may also wish to know the risk of having additional children with retinoblastoma. Additionally, ophthalmologists may examine patients who survived hereditary retinoblastoma and are at increased risk to develop other cancers, particularly osteosarcoma originating in an irradiated orbit.2,3 Recently, we reported the successful development of laboratory procedures based on the cloned retinoblastoma gene that can often identify individuals who carry a mutation predisposing to hereditary retinoblastoma.4 Herein we describe the application of genetic testing to the different clinical situations that the ophthalmologist may face. Know-

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ing the value of the gene testing in different clinical situations will allow the ophthalmologist to decide when to order the test and how to interpret the results.

In order to provide a basis for the discussion of genetic testing, we will first describe the current knowledge of the retinoblastoma gene and its role in tumor formation. The normal protein encoded by the retinoblastoma gene appears to prevent the formation of certain malignancies, such as retinoblastoma, osteosarcoma, and certain soft tissue sarcomas. Malignant transformation of a retinal cell occurs when both homologous copies of the retinoblastoma gene (that is, both the maternally and paternally derived copies) in that cell have loss-of-function mutations. 5-7 One normal copy of the gene is adequate to prevent tumor formation. Thus, retinoblastoma is one of a group of human cancers that are caused by loss-offunction mutations at distinct genetic loci, termed recessive oncogenes.

About 10% to 30% of the mutations predisposing to retinoblastoma are the result of deletions, some of which are detectable by karyotyping. If the defective copies of the gene in tumor cells are the result of "somatic mutations," which are mutations occurring only in the retinal cell that gave rise to the tumor, then the patient develops nonhereditary retinoblastoma. Alternatively, if the patient inherits one mutant copy of the gene from an affected parent and a somatic loss-of-function mutation occurs in the gene copy from the normal parent, then a hereditary retinoblastoma will result. A patient can also receive a mutant copy of the retinoblastoma gene as a new germinal mutation. There is no known histopathologic feature present in tumor cells that will distinguish hereditary from nonhereditary retinoblastoma.8

Clinical features of patients with retinoblastoma can occasionally be used to identify patients with hereditary disease (Table 1). Retinoblastomas that are caused by two somatic mutations are always nonhereditary and unilateral. In this group only the retinoblastoma tumor cells carry mutations; the copies of the retinoblastoma gene in the germ cells are normal. Conversely, patients with hereditary retinoblastoma have a germ line mutation (every bodily cell, including gonadal stem cells, carries a mutation) of one copy of the retinoblastoma gene. Germ line mutations can be transmitted to future offspring. Half of the children of patients with hereditary retinoblastoma will

TABLE 1
CLINICAL CHARACTERISTICS OF RETINOBLASTOMA

TUMOR TYPE	FAMILY HISTORY	NONHEREDITARY	HEREDITARY
Unifocal	No	85–95%	10-15%
	Yes	0%	100%
Multifocal or	No	0%	100%
bilateral	Yes	0%	100%

inherit the mutation from the involved parent, and of these, 90% will sustain a subsequent mutation of the remaining normal copy of the gene in at least one retinal cell and develop retinoblastoma. Most patients (60%) who inherit a mutant copy of the retinoblastoma gene or who have a new germ line mutation develop bilateral retinoblastoma. Genetic analysis is not required to establish the hereditary nature of these cases, but rather to examine the transmission of the mutant copy of the retinoblastoma gene to the offspring. However, 30% of these patients develop unilateral retinoblastoma and 10% of them do not develop retinoblastoma at all but remain asymptomatic carriers of the mutant disease gene. With these patients an initial goal of genetic analysis is to separate these cases from the nonhereditary cases described above.

Currently, all children of parents with hereditary retinoblastoma receive ophthalmoscopic examinations that require general anesthesia every three months during their first years of life. The laboratory testing regimen we have developed, based on the cloned retinoblastoma gene, can identify persons who have inherited a tumor-predisposing mutation so that these examinations can focus on children who indeed carry a mutant copy of the gene and would reduce or eliminate the need for such examinations in children thought to have a normal genotype.

Before informative genetic testing could be developed, the retinoblastoma gene had to be identified and isolated. The observation that mutations in a particular region of chromosome 13 correlated with retinoblastoma was the first step in accomplishing this goal. Using molecular genetics techniques, the precise locus that governed the development of retinoblastoma within chromosome 13 was identified. Once the location of the gene was known, the DNA sequences that compose the gene were cloned, thereby making them available for laboratory manipulation. The retinoblastoma gene is quite

large (approximately 200,000 base pairs of DNA), and mutations occurring in many different locations within the gene can result in retinoblastoma. An ideal laboratory test designed to identify individuals at increased risk for retinoblastoma would detect the actual tumor-predisposing mutations in the gene. Unfortunately, only mutations caused by deletions of the genomic DNA can be shown by a practical method such as Southern blotting. In our analysis of 20 families with hereditary retinoblastoma, only three had such detectable mutations. Most tumor-predisposing mutations are the result of small DNA abnormalities that may ultimately require DNA sequence analysis for detection. It is not practical with current technology to sequence both copies of the gene from every patient in question. However, naturally occurring DNA sequence variations that are unrelated to retinoblastomapredisposing mutations can be used as markers to tag the chromosome that carries the mutation. These sequence variations are detected by digesting DNA with restriction enzymes and hence are called restriction fragment length polymorphisms.¹⁰ There are at least seven restriction fragment length polymorphisms within the retinoblastoma gene. If a restriction fragment length polymorphism can be shown to be linked to (or in phase with) a mutant copy of the gene in a particular family, then the restriction fragment length polymorphism (and thereby the mutation) can be traced through the pedigree.

Restriction fragment length polymorphisms are valuable tools for analysis when deletions are not present. The usefulness of this technique is dependent on the structure of the pedigree in question. The most information for genetic counseling is obtained from large families with multiple family members affected so that the linkage of a certain marker to the mutant gene can be established. However, there are other situations where only a few family members are available, yet one can accurately determine the risk for retinoblastoma in some family members. Most clinical problems can be represented by the pedigrees shown in the Figure.

Families With Multiple Cases of Retinoblastoma

Among the patients with hereditary retinoblastoma are those who have unilateral or bilateral retinoblastoma and have a parent, sibling, or more distant relative affected as well. Each offspring produced by these patients has a 45% chance of developing retinoblastoma (50% chance of inheriting the mutation; mutations have a penetrance of 90%). The pedigree of a small family with hereditary retinoblastoma is shown in the Figure, A. The goal of genetic testing in families with hereditary retinoblastoma is to identify those individuals who carry a mutation and are at risk for tumor development. In 15% of families with hereditary retinoblastoma it is possible to detect the tumorpredisposing mutation itself. Most mutations detectable by Southern blotting are deletions that range in size from a few hundred base pairs to over 200,000 base pairs. Only deletions of more than two million base pairs of DNA can be seen by high resolution chromosome banding. Approximately 100 million base pairs of DNA are contained in an average sized chromosome, such as chromosome 13. When a detectable deletion is present, one can identify individuals carrying the mutation with a confidence greater than 99%.

In the remaining 85% of families with hereditary retinoblastoma no mutation can be found directly. However, in 95% of these families with more than one affected, living family member it is still possible to deduce the copy of the gene that carries the tumor-predisposing mutation by finding a restriction fragment length polymorphism marker that the affected family members share. For example, in the pedigree shown (Figure, A) the two homolo-

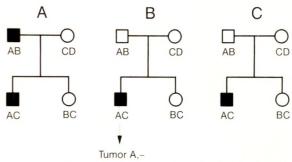


Figure (Wiggs and Dryja). Representative pedigrees of families with retinoblastoma. The affected individuals are shown as solid squares (males) or circles (females). A, hereditary retinoblastoma with two affected family members; B, simplex retinoblastoma with tumor available for analysis; C, simplex retinoblastoma. Marker restriction fragment length polymorphism alleles are noted for each family member by letters. Solid circles or squares represent affected individuals.

gous copies of the gene in the affected father are found to have different restriction fragment length polymorphism markers called A and B and the normal mother has restriction fragment length polymorphism markers C and D. The first child develops retinoblastoma and we find that he has inherited the gene copy (allele) with marker A from his father and marker C from his mother. We infer that marker A tags the paternal gene copy that carries the retinoblastomapredisposing mutation in this family. Once a marker is known to be linked with the mutation predisposing to the tumor, all remaining members of a pedigree can be tested to determine if they carry the mutant allele. The predictions based on this analysis have an accuracy of at least 90% and are probably over 98% accurate.

Families With a Single Case of Retinoblastoma

All patients with retinoblastoma who have a negative family history can be conveniently called simplex cases, whether they have the hereditary or nonhereditary type of retinoblastoma. All such patients with bilateral disease have hereditary retinoblastoma. Most unilateral simplex cases have nonhereditary disease, but 10% to 15% have the hereditary type (Table 1). A patient with hereditary retinoblastoma without a family history either has a new germ line mutation or one of the patient's parents is an asymptomatic carrier of a mutation.

A common clinical problem is to decide which unilateral simplex cases have hereditary retinoblastoma. Some simplex patients with unilateral, hereditary retinoblastoma can be identified clinically if they develop a second neoplasm related to the retinoblastoma gene, such as pinealoblastoma or osteosarcoma. This, however, is uncommon. Genetic testing of families with a single affected member can sometimes help identify those who have hereditary disease. If a tumor-predisposing mutation is demonstrated, then genetic analysis can identify the family members who carry the mutation. Yet, even with the cloned retinoblastoma gene, deciding whether unilateral, simplex cases have hereditary or nonhereditary retinoblastoma is often not feasible with current techniques.

Even if it is not possible to determine if a patient has hereditary disease, retinoblastoma gene testing can play a role in better determining the risk for retinoblastoma in the siblings of the patient. This is important because 6% to 12% of patients with unilateral or bilateral simplex retinoblastoma develop the tumor because

one of the parents happens to be an asymptomatic carrier of a mutant copy of the retinoblastoma gene. As a result, an unaffected couple who have one child with retinoblastoma, whether unilateral or bilateral, have a 1% to 6% chance of having a second child affected with the tumor. In many clinical situations the risk of tumor development in the future offspring can be established with greater accuracy using analysis based on the retinoblastoma gene.

Examination of leukocyte DNA will show a deletion of the retinoblastoma gene in 10% to 15% of simplex bilateral retinoblastoma and in 1% of simplex unilateral retinoblastoma. In such instances, the leukocytes from parents and siblings can be checked for the deletion. All family members with the deletion either have hereditary retinoblastoma or are asymptomatic carriers. In the remaining 85% to 99% of cases, one must rely on tagging the chromosome that carries the mutation. In simplex cases this is difficult with marker restriction fragment length polymorphisms because the phase (linkage) between the restriction fragment length polymorphism markers and the potential, germ line tumor-predisposing mutation cannot be established without additional affected family members. However, there are several special instances where genetic risks can be determined for some family members based on a fortunate distribution of restriction fragment length polymorphism markers or on the examination of a fresh tumor fragment.

For example, in about 50% of patients with simplex retinoblastoma, the analysis of tumor DNA (in addition to analysis of leukocyte DNA) can allow the identification of the chromosome potentially carrying a tumor-predisposing mutation. This is because approximately 50% to 70% of tumors originate from a retinal cell that loses the chromosome carrying the normal copy of the retinoblastoma gene. 11 Since the tumor is a clone of cells derived from the aberrant progenitor, every tumor cell will similarly have only one chromosome 13, which is the one with the potential germ line mutation. Therefore, any restriction fragment length polymorphism marker present in the tumor cells must tag, or be in phase with, the potential germ line mutation.

Analysis of tumor DNA consequently greatly enhances the information available for genetic counseling. For example, Figure, B shows a pedigree with one child affected with bilateral retinoblastoma. As stated above, this child either represents a new germ line mutation or

one of his parents is an unaffected carrier of a tumor-predisposing mutation. Analysis of the marker restriction fragment length polymorphisms present in the leukocyte DNA of the family members alone does not demonstrate which copy of the retinoblastoma gene in the affected child carries a mutation. However, analysis of the tumor DNA shows that the copy of the gene marked by the A allele is present in the tumor DNA but the gene copy carrying the C allele is absent. Because the tumor develops when the last remaining normal copy of the gene is lost, this result implies that the copy of the gene still present in the tumor (marked by the A allele) is the mutant copy. From this information we can predict that only individuals who carry this copy of the retinoblastoma gene are at increased risk for retinoblastoma. Since the father is the origin of the marker restriction fragment length polymorphism allele, he is a potential asymptomatic carrier, while the mother definitely is not. If the father is an unaffected carrier, then all of his children who don't inherit his A allele are at low risk for tumor development.

If the affected child in Figure, B had unilateral retinoblastoma, there is a 10% to 15% chance that this child has the hereditary disease. If tumor tissue is available, an analysis identical to that just described could be performed in such a family to rule out the risk of retinoblastoma in some of the siblings.

Even if no tumor tissue is available, the analysis of a pedigree with a single affected child can in some cases provide useful information concerning the risk of retinoblastoma developing in the patient's siblings. For example,

in the pedigree outlined in Figure, C the younger sibling shares no parental retinoblastoma alleles with his affected brother. This will occur in 25% of the siblings of an affected child.10 Thus, even if one parent were an asymptomatic carrier of a tumor-predisposing mutation, the mutant allele could not be shared by the affected child and the unaffected sibling. Hence, in such a situation, one can determine that the normal sibling is at low risk for developing retinoblastoma or of having children affected with retinoblastoma. It is important to note that this evaluation does not help the offspring of the affected simplex patient, since one cannot demonstrate which marker allele is linked to the tumor-predisposing mutation in the affected individual (unless tumor tissue is available, as discussed above).

Indications for Genetic Testing

Genetic testing is most useful for families with at least two affected members (Table 2). In 95% of such families, retinoblastoma gene testing can accurately identify individuals who have a tumor-predisposing mutation and who will develop retinoblastoma or will be unaffected carriers. One percent of simplex families with unilateral retinoblastoma and 10% of simplex families with bilateral disease have hereditary retinoblastoma caused by a sufficiently large deletion of the gene so that examination of leukocyte DNA will demonstrate the tumorpredisposing mutation. Among families with only one affected member, one can identify the 25% of unaffected siblings who do not share any possible tumor-predisposing mutation with the affected sibling and are therefore not

TABLE 2
RETINOBLASTOMA GENE TESTING IN AFFECTED FAMILIES

NO. OF AFFECTED FAMILY MEMBERS	TUMOR TYPE	GENETIC TYPE	% OF FAMILIES WITH IDENTIFIABLE MUTATIONS IN AN AFFECTED INDIVIDUAL	% OF UNAFFECTED SIBLINGS IDENTIFIABLE AS NONCARRIERS OF A MUTATION
Two or more	Unilateral or bilateral	Hereditary	95	95
One	Multifocal or unifocal with a secondary tumor	New germ line mutation (hereditary)	10*	25
One	Unilateral only	90% somatic mutation (nonhereditary) 10% germ line mutation	1*	25

^{*}Increases to 25% if tumor DNA is available for analysis.

at high risk to develop retinoblastoma. If tumor DNA is available for analysis, the fraction of all families for which useful genetic counseling information can be provided is greatly increased.

The use of retinoblastoma gene testing to identify individuals at risk for tumor development has two limitations. First, the analysis requires that certain key family members, usually the affected parents, have different markers present in the retinoblastoma gene. We have identified sufficient restriction fragment length polymorphism sites so that approximately 95% of families will meet this criterion for the analysis. Second, the site of the marker restriction fragment length polymorphism within the retinoblastoma gene and the precise site of the mutation causing the disease are not identical and rarely the two DNA sequences may not be inherited together. The chance that a meiotic recombination event will occur between the mutation and the marker site is small, but it does take away from the overall accuracy of the test.

The procedure for handling eyes enucleated for retinoblastoma so that tumor fragments can be saved for genetic analysis is as follows: (1) the tumor should be larger than 5 mm in diameter; (2) the globe should not be placed in fixative until the tumor fragment is harvested; (3) the end of the optic nerve should be excised and placed in a separate jar of formalin; (4) the eye should be sectioned in a plane determined by the pupil, optic nerve, and tumor, so that the tumor is bisected; (5) the section of the eye containing the optic nerve and one half of the tumor should be placed in a second jar of formalin; and (6) several cubic millimeters of tumor from the remaining half of the eye should be harvested and stored at -70 C. The harvested tumor should be sent to the testing laboratory frozen on dry ice.

Restriction fragment length polymorphisms present within the cloned human retinoblastoma gene are valuable for the genetic counseling of many retinoblastoma patients and their relatives. Gene testing can identify individuals at risk for tumor development in the majority of families with hereditary retinoblastoma. In families with a single member affected by the tumor, retinoblastoma gene testing can demonstrate the tumor-predisposing mutation in a small percentage of cases. In those simplex cases where such a mutation can be detected, the family members who are at increased risk for retinoblastoma can be identified. All fami-

lies with simplex cases should be tested, however, since 25% of siblings of an affected child can be shown to be free of a retinoblastoma-predisposing mutation. In all families, including those with simplex retinoblastoma, the analysis of tumor DNA can significantly increase the percentage of identifiable tumor-predisposing mutations. Future work will be directed toward increasing the accuracy of the current test for hereditary retinoblastoma and developing new techniques which could make the genetic counseling of simplex retinoblastoma more informative.

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LETTERS TO THE JOURNAL

Afferent Pupillary Defect Caused by Hyphema

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A relative afferent pupillary defect usually indicates optic nerve disease. This sign can also be caused by dysfunction elsewhere in the visual pathway from the retina to the Edinger-Westphal nuclei in the midbrain. However, an afferent pupillary defect is not thought to be caused by media opacities such as cataracts or intraocular hemorrhages, both of which act as light diffusers; a pupillary defect associated with such opacities should lead one to suspect that a second lesion may be found along the anterior visual pathway. We encountered two patients with total hyphemas associated with marked relative afferent pupillary defects. In both cases, no other cause could be found for the pupillary defect. The disappearance of the afferent defect coincided with the resolution of the hyphema and left the patients with normal vision and no signs of optic atrophy.

Case 1

A 16-year-old girl was struck in the left eye four days before examination. Her vision had

been hazy but acutely worsened on that day. She had taken aspirin for pain and photosensitivity. Visual acuity was 20/20 in the right eye and light perception with projection in the left eve. A marked left afferent pupillary defect was detected by observing the right eye. The left anterior chamber was filled almost entirely with blood, and a large clot obscured the pupil. Motility was full and there was no evidence of orbital hemorrhage. Intraocular pressure was 12 mm Hg in the right eye and 25 mm Hg in the left. No view of the fundus was possible. Ultrasonography demonstrated a normal posterior segment and optic nerve. She was treated with oral aminocaproic acid, and the aspirin was discontinued. A second episode of bleeding was noted on the fourth hospital day. As the clot and hyphema gradually resolved, the afferent defect disappeared and visual acuity improved to 20/20. She had a full visual field by kinetic perimetry and a normal fundus appearance with a healthy optic disk.

Case 2

A 7-year-old boy was struck in the left eye by a rock four days before examination. The parents sought medical attention when the boy's eye became painful and injected. Visual acuity was 20/20 in the right eye and light perception in the left eye. A total hyphema was noted but there was no motility defect or other evidence of an orbital hemorrhage. There was a left afferent pupillary defect detected by observing the right eye. Intraocular pressure was 30 mm Hg in the left eye. The patient was treated with oral aminocaproic acid and topical timolol. The clot slowly resolved and the aminocaproic acid was discontinued on the sixth hospital day. A

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second episode of bleeding occurred and intraocular pressure increased to 45 mm Hg. The boy was treated with acetazolamide and aminocaproic acid. The cornea developed microcystic changes and the hyphema was removed surgically. Postoperatively, visual acuity in the left eye improved to 20/20 and the afferent pupillary defect resolved. The retina and the optic disk have a normal appearance.

The relative afferent pupillary defects in these two patients seem to have been caused by the hyphemas. In both cases, the pupillary defect gradually resolved as the anterior chamber cleared. There were no signs of other anterior visual pathway lesions known to cause afferent defects such as retinal detachment, acute glaucoma, optic neuropathy, or retrobulbar hemorrhage. We believe that the dense blood in the anterior chamber had the effect of reducing, rather than diffusing, the light entering the eye. This resulted in an afferent defect

similar to the one that is created by placing neutral density filters before an eye.

Blood in the posterior segment of the eye may have a similar effect. Abrams and Knighton² described three patients with dense vitreous hemorrhages who had nonrecordable bright-flash electroretinograms. After vitrectomy, substantial visual recovery and partial improvement in the electroretinogram was seen. The authors did not comment on the pupillary reactions. It is possible that a nonrecordable electroretinogram is analogous to an afferent pupillary defect.

Detecting an afferent pupillary defect in a patient with a dense hyphema should alert the clinician to suspect optic nerve or retinal damage. However, this sign may be related solely to dense intraocular blood and does not preclude excellent visual recovery. An afferent defect should not dissuade the physician from aggressive intervention in hyphema management.

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Acute Primary Closed-Angle Glaucoma Associated With Hyphema

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Increased intraocular pressure associated with a nontraumatic hyphema strongly suggests neovascular glaucoma. We treated a patient with acute primary closed-angle glaucoma without evidence of neovascular glaucoma.

A 58-year-old woman had blurred vision in her right eye for ten days (which had worsened after four days), redness, and supraorbital pain. Her vision while watching television in a darkened room had been blurring intermittently for at least six months. The patient did not have a history of diabetes.

Results of examination showed right upper eyelid edema and bulbar conjunctival injection. Visual acuity in the right eye was counting fingers at 1 foot. The applanation pressure was 67 mm Hg. The pupil measured 6 mm and was nonreactive. An afferent pupillary defect was noted. Slit-lamp biomicroscopy showed diffuse microcystic corneal edema, a shallow anterior chamber containing a 3-mm hyphema, and a patch of tortuous vessels on the superonasal peripupillary iris surface. Persistent corneal edema and the hyphema prevented gonioscopy. Ophthalmoscopy showed a physiologically cupped nerve with retinal venous engorgement, cotton-wool spots, and peripapillary intraretinal hemorrhages (Fig. 1).

Visual acuity in the left eye was 20/40, with an intraocular pressure of 18 mm Hg. On gonioscopy, a shallow anterior chamber and a markedly convex peripheral iris were noted as well as an open angle without synechiae on compression. The fundus was unremarkable.

Results of carotid artery examination, including palpation and ultrasonography, did not show any significant stenosis.

The patient was treated with 0.5% timolol maleate in the right eye, 2% pilocarpine hydrochloride in both eyes, and 500 mg of acetazolamide orally and 250 mg of acetazolamide intravenously. Overnight medications included 1% prednisolone acetate in the right eye, 500 mg of

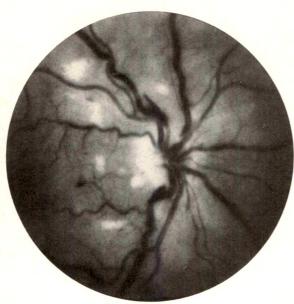


Fig. 1 (Cashwell and Croyle). Fundus photograph of the right eye demonstrates scattered cotton-wool spots and intraretinal hemorrhages.

oral acetazolamide, and the timolol maleate and pilocarpine hydrochloride.

Examination of the right eye 24 hours later showed unchanged visual acuity, an intraocular pressure of 41 mm Hg, and a clot on the iris inferior to the tortuous vessels (Fig. 2). An iridotomy was created with the YAG laser. Treatment with dipivefrin hydrochloride was begun.

Over the next five days, the corneal edema and hyphema persisted. Intraocular pressure remained increased from 49 to 54 mm Hg and

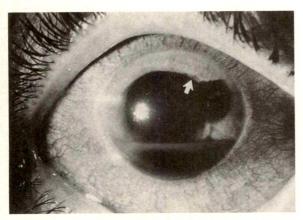


Fig. 2 (Cashwell and Croyle). Slit-lamp photograph of the right eye shows hyphema with old, dark blood inferiorly and fresh blood, not seen previously, on top. Note tortuous vessels at the 1 o'clock meridian at pupil (arrow), and the clot on the iris surface inferior to the vessels.

the angle closure persisted. A trabeculectomy with anterior chamber washout was performed three days later. Four days postoperatively intraocular pressure was 3 mm Hg in the right eye and 11 mm Hg in the left eye. Argon laser iridotomies were created in the left eye.

Twenty-seven months later, best-corrected visual acuity was 20/20 bilaterally. Intraocular pressure was 15 mm Hg in the right eye and 19 mm Hg in the left eye. The right eye had a functioning filtering bleb and no abnormal iris vessels. Complete synechial angle closure persisted, and perimetry showed nasal contraction. The right optic nerve was paler than the left. The arteriolar-venular ratio was 1 to 2 in both eyes.

The cotton-wool spots, intraretinal hemorrhages, and spontaneous hyphema in our patient suggested neovascular glaucoma. However, because the patient had normal vision until the acute attack, this diagnosis was incompatible with that diagnosis, and no additional findings supported it. The decrease in vision after the acute attack and the new clot seen later were consistent with hyphema from iris vessels engorged and inflamed by closed-angle glaucoma.

The extreme narrowness of the contralateral anterior chamber angle suggested intermittent angle closure in the right eye. We believe that in our case, the absence of secondary causes of closed-angle glaucoma supports the diagnosis of primary closed-angle glaucoma with subsequent hyphema. This conclusion contrasts with that of Perry, Mallen, and Sussman, who concluded that a spontaneous hyphema from a preexisting iris microhemangioma had precipitated an acute attack of glaucoma.

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Cyanide Poisoning Victims as Corneal Transplant Donors

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Ingestion of soluble, inorganic cyanide salts results in death by inhibition of cellular respiration at the mitochondrial level, causing cytotoxic hypoxia. The extreme toxicity of cyanide is caused by its ready reaction with the trivalent iron of cytochrome oxidase in mitochondria to form the cytochrome oxidase-CN complex. We encountered two patients who died as a result of cyanide poisoning whose corneas were used for corneal transplantation.

An autopsy was performed on a 52-year-old man with a history of chronic obstructive pulmonary disease. The cause of death was stated to be respiratory failure.

An autopsy was performed on a 42-year-old woman by order of the Medical Examiner's Office to determine the cause of death. A bitter almond odor was noted during the autopsy. Analysis of serum sent to the state toxicology laboratory showed cyanide levels consistent with acute cyanide poisoning as the cause of death. Because the deaths of the two patients were temporally related, the Medical Examiner's Office wished to examine bodily fluids from the man. Because no bodily fluids were available, the Lions' Eye Bank provided serum drawn for virology testing. Toxic levels of cyanide were found and cyanide poisoning was confirmed as the cause of death in this case as well. Subsequent investigation confirmed that the source of the cyanide was acetaminophen capsules that had undergone tampering.

The four patients receiving donor corneas from the victims of cyanide poisoning have all been followed up for at least 18 months postoperatively. Indications for penetrating keratoplasty were Fuchs' dystrophy in two patients and pseudophakic bullous keratopathy in two patients. All corneal transplants have remained thin and clear since surgery. Postoperative visual acuities were as follows: 20/40 in one patient, 20/60 in two patients, and 20/200 in one patient with preexisting age-related macular degeneration.

Robbie, Leinfelder, and Duane³ showed that cyanide readily inhibits cellular respiration in excised pieces of cornea, but that spontaneous recovery of oxygen consumption occurs after several hours if glucose is available in the medium. Cyanide blocks the reduction of oxygen catalyzed by cytochrome oxidase. Cyanide binds to iron in the ferric (trivalent) state of

cytochrome oxidase in mitochondria to form the cytochrome oxidase-CN complex, which is dissociable. Recovery of respiration upon the removal of cyanide is rapid.³ Experimentally, sections of cornea removed from cyanide solution and washed in a buffer showed nearly the same oxygen uptake as the control cornea within 15 minutes after rinsing. Additionally, most oxygen consumption of the intact cornea is due to the epithelial layer, which would further minimize the risk of using cyanide poisoning victims as donors for corneal transplantation.

Victims of cyanide poisonings are suitable as corneal transplant donors, provided the corneoscleral tissue is rinsed thoroughly and maintained in a tissue-storage medium containing glucose. McCarey-Kaufman medium, K-Sol solution, and chondroitin-containing corneal storage medium all contain adequate levels of glucose to maintain cellular respiration.

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Conjunctival Z-Plasty in the Treatment of Pterygium

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Many surgical procedures have been described for the treatment of pterygium including some variation of excision, redirection, or irradiation. After the pterygium is excised, the resulting defect can be managed in a variety of ways. Several methods have been described in which the surrounding conjunctiva is undermined and rotated into the resulting defect. Alternatively, the defect can be preserved in one of the variations of the bare sclera tech-

nique. More recently, autologous conjunctival transplantation has been advocated, especially in the treatment of advanced or recurrent pterygia. 2,3

We have adopted recently a variation of the conjunctival Z-plasty technique for the treatment of primary pterygia. Initially described by Stocker4 in 1942, the Z-plasty technique has received little attention in the literature since its publication. We have found this method to be both simple and effective. This procedure allows for the combined removal of pathologic tissue from the cornea and the rotation of a flap of more normal conjunctiva into the resulting defect. This provides a barrier to the regrowth of the pterygium onto the cornea. Another advantage is the preservation of the conjunctiva for use in the more extensive conjunctival autograft procedure in the event of a recurrence.

In our modification of the original technique, 5-0 silk limbal fixation sutures are placed superiorly and inferiorly, and the globe is rotated into

the most advantageous position. The conjunctiva is dried, and the intended lines of incision of the Z-plasty are drawn with a gentian violet marker (Fig. 1, top left). Note that the incisions are to be extended along the corneoscleral limbus above and below the involved area. Both angles of the Z should be equal. We have found approximately 45 degrees to be optimal. Although we directed the Z-plasty incision inferiorly, it may be directed superiorly, however, depending on the position of the pterygium and the preference of the surgeon. The head of the pterygium is then dissected from the cornea and excised at the corneoscleral limbus. The conjunctiva and underlying subconjunctival tissues are incised to the sclera with straight scissors along the drawn lines, forming the flaps of the Z-plasty incision. The flaps are dissected from the underlying sclera with the scissors. Surrounding conjunctiva should also be undermined to allow for free mobility of the flaps (Fig. 1, top right). The flaps are rotated so that the peripheral flap (B) of more normal

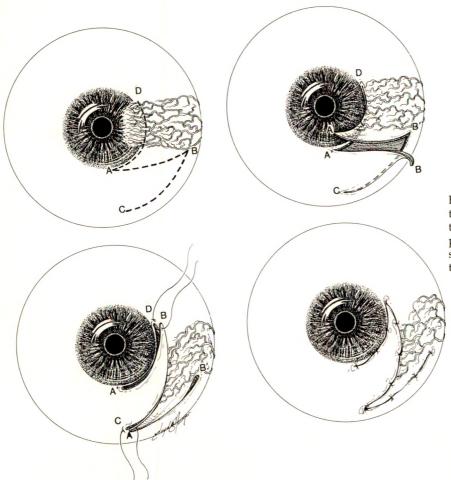


Fig. 1 (Wilson and Bourne). An illustration of the conjunctival Z-plasty technique in the treatment of pterygium. The individual steps are described in the text.

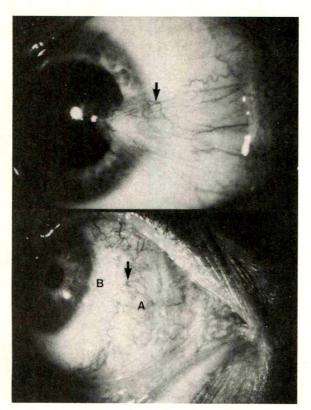


Fig. 2 (Wilson and Bourne). Top, Preoperative photograph of a pterygium. Bottom, Two weeks after conjunctival Z-plasty. Flap A contains the remaining tissues of the pterygium and flap B is composed of more normal conjunctiva. The arrow in each photograph indicates a vascular loop, which illustrates the posterior rotation of the remaining tissues of the pterygium.

conjunctiva is brought into a position (D) adjacent to the corneoscleral limbus and the central flap (A) containing the remaining tissues of the pterygium is rotated posteriorly (C) away from the corneoscleral limbus (Fig. 1, bottom left). Next, 9-0 Vicryl on a spatula needle is used to fix the flaps into position with interrupted sutures (Fig. 1, bottom right). The needle is passed into the episcleral tissues to insure fixation of the flaps. The ends of the suture are cut on the knot.

Note the representative photographs taken before and two weeks after the Z-plasty operation (Fig. 2).

The conjunctival Z-plasty technique is useful for the treatment of primary pterygia. In the event of a recurrence, a conjunctival autograft could then be considered. Ocular surgeons should be aware of Stocker's contribution to the treatment of pterygia.

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Ciliochoroidal Detachment Associated With Stretched Ciliary Processes

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Hypotony and ciliochoroidal detachments have a limited number of causes. Geyer, Godel, and Lazar¹ reported a single case of hypotony and ciliochoroidal detachment after phacoemulsification associated with visible traction on ciliary processes adherent to the posterior capsule and lens remnants. Surgical capsulotomy was curative. We had a similar case that confirms these observations, and supports the concept of ciliary body traction as a new cause of ciliochoroidal detachment.

A 74-year-old man underwent an uncomplicated extracapsular cataract extraction with posterior chamber intraocular lens implantation in the right eye. He had previously undergone an uneventful cataract extraction with an anterior chamber intraocular lens implantation in the left eye. He had a ten-year history of primary open-angle glaucoma that was well controlled on timolol 0.5%.

The patient did well for five weeks postoperatively, with unrefracted visual acuity of 20/40 and intraocular pressures more than 15 mm Hg after treatment with timolol. He then complained of a shadow in his peripheral vision.

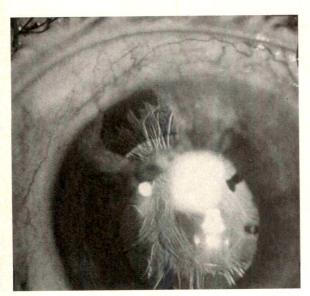


Fig. 1 (Magruder and Harbin). Precapsulotomy photograph demonstrating zonular traction on ciliary process.

His visual acuity was 20/40 and his intraocular pressure was 8 mm Hg. The anterior chamber was slightly shallow and a choroidal detachment was noted. There was no evidence of a wound leak. Timolol was discontinued. Three days later ciliary processes were noted to be stretched centrally as seen through the peripheral iridectomy (Fig. 1). Central posterior capsule opacification was present. Gonioscopy failed to show a cyclodialysis cleft. The choroidal detachment was larger.

One week later, visual acuity was 20/50 and the intraocular pressure was 6 mm Hg. The patient underwent Nd:YAG laser capsulotomy. Traction on the ciliary processes was relieved (Fig. 2). Two days later, visual acuity was 20/30+, intraocular pressure was 22 mm Hg, and the anterior chamber was deeper. The choroidal detachment resolved.

This patient developed hypotony and ciliochoroidal detachment five weeks after extracapsular cataract extraction with posterior lens implantation. This was associated with posterior capsule opacification and traction on ciliary processes. An Nd:YAG laser capsulotomy relieved traction, hypotony, and choroidal detachment. The observations are consistent with ciliary body traction as a cause of ciliochoroidal detachment.

We have observed that intraocular pressures are lower in many eyes after extracapsular cataract extraction. In some cases, ciliary body traction may be responsible for this phenomenon.

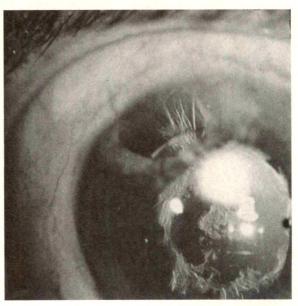


Fig. 2 (Magruder and Harbin). Postcapsulotomy photograph demonstrating resolution of ciliary process traction.

Ciliary body traction should be included in the differential diagnosis of hypotony and ciliochoroidal detachment occurring months after extracapsular cataract extraction or phacoemulsification. Consideration should be given to laser capsulotomy, even if lack of a peripheral iridectomy precludes direct visualization of ciliary processes.

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Occult Suprachoroidal Hemorrhage and Posterior Scleral Rupture

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Suprachoroidal hemorrhage is a potential sequela of almost every type of intraocular surgery, which rarely occurs spontaneously. In an unoperated on eye, suprachoroidal hemorrhage is usually associated with perforation of a corneal ulcer or the presence of an anterior staphyloma and glaucoma. Spontaneous suprachoroidal hemorrhage with scleral rupture can mimic primary orbital disease if the staphylomatous defect is situated posteriorly.

A 92-year-old woman with a history of organic brain syndrome was noted by nursing home personnel to have suddenly developed swelling of her left upper and lower eyelids. The patient had been blind in both eyes for many years, presumably from glaucoma. The patient was unable to provide any additional history. On examination she could not perceive light with either eye. The left globe was 4 mm proptotic and both eyelids were swollen. The conjunctiva was edematous, inflamed, and hemorrhagic. The anterior chamber was deep and without signs of inflammation. The posterior pole could not be seen because of a mature cataract. By finger ballottement, intraocular pressure in each eye seemed within the range of normal. Results of general examination of the remainder of the eye were normal, and routine laboratory studies yielded no additional pertinent information. Computed tomography and ultrasonography of the eye and orbit disclosed abnormal densities within the vitreous cavity, but because of lack of patient cooperation, optimal studies could not be obtained.

It was suspected that a primary intraocular process was related to the inflammatory orbital condition. Both infectious and noninfectious causes of endophthalmitis were considered in the differential diagnosis. Because the left eye had no vision, enucleation was performed to establish a diagnosis and to alleviate patient discomfort.

Results of pathologic examination of the globe disclosed a circumferential staphyloma of the equator that had ruptured superiorly beneath the superior rectus muscle (Figure). A massive suprachoroidal hemorrhage originating from ciliary vessels located inferiorly had forced choroid, retina, and vitreous through the superior scleral defect into the orbit. Granulation tissue surrounded the prolapsed ocular tissue.

Massive spontaneous suprachoroidal hemorrhage associated with scleral rupture is extremely rare. We speculate that the sclera may have ruptured initially in this staphylomatous eye, causing rapid decompression of the globe

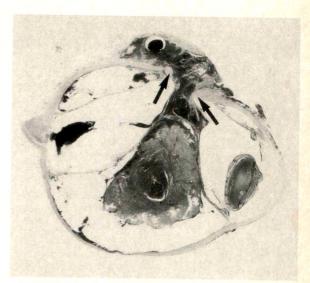


Figure (Margo, Bullington, and Pautler). Sagittal section through left eye shows a large hemorrhage originating inferiorly in the suprachoroidal space that has pushed retina, vitreous, and choroid through a superior scleral defect (arrows) at the equator (hematoxylin and eosin, ×2.3).

and displacement of the choroid. Because ciliary vessels are fixed to the sclera, any substantial movement of the choroid relative to the sclera presumably could lead to a tractional vascular tear.

Many factors are associated with suprachoroidal hemorrhage after surgery, including glaucoma, a patient's age greater than 60 years, generalized atherosclerotic vascular disease, and sudden decompression of the eye. These same factors are probably related to the pathogenesis of spontaneous suprachoroidal hemorrhage. Spontaneous suprachoroidal hemorrhage should be considered in the differential diagnosis of acute proptosis, especially if the posterior segment cannot be visualized and ectasia or rupture of the sclera is demonstrable by computed tomography or ultrasonography.

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Epidemic Keratoconjunctivitis Associated With Blepharoptosis

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Epidemic keratoconjunctivitis is an adenoviral infection of the cornea and conjunctiva. Complications of this disease include subepithelial infiltrates, iritis, and conjunctival pseudomembranes. ¹⁻³ An outbreak of more than 200 cases of epidemic keratoconjunctivitis occurred in the Hamilton, Ontario, area in the fall of 1986. Two patients were referred to our Oculoplastic Service for evaluation of blepharoptosis developing after epidemic keratoconjunctivitis.

Case 1

An 18-year-old woman developed epidemic keratoconjunctivitis in October 1986. She had bilateral eyelid swelling, with the left eyelid more severely affected than the right. She was referred for evaluation of an acquired left upper eyelid blepharoptosis. Family photographs showed no evidence of blepharoptosis

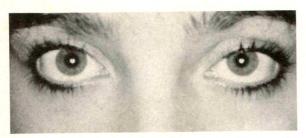


Fig. 1 (Corin and Harvey). Case 1. An 18-year-old woman with 1 mm of left upper eyelid blepharoptosis after epidemic keratoconjunctivitis infection.

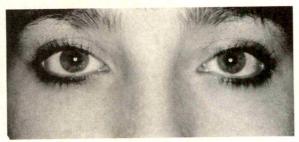


Fig. 2 (Corin and Harvey). Case 1. Two months after Fasanella-Servat for correction of left upper eyelid blepharoptosis.



Fig. 3 (Corin and Harvey). Case 2. A 77-year-old woman with 2 mm of right upper eyelid blepharoptosis after epidemic keratoconjunctivitis infection.

before the infection. On examination, palpebral fissures were 11 mm on the right and 10 mm on the left. Levator function was 15 mm on each side. The eyelid crease was noted to be higher on the left upper eyelid than on the right (Fig. 1). She underwent a successful Fasanella-Servat blepharoptosis repair in August 1987 (Fig. 2).

Case 2

A 77-year-old woman developed epidemic keratoconjunctivitis in December 1986. She had a severe case with subepithelial infiltrates bilaterally and swelling of all four eyelids. After the infection, she noted that her upper eyelids were droopy, with the right eyelid lower than the left. On examination, her palpebral fissures were 7 mm on the right and 9 mm on the left (Fig. 3). Levator function was 15 mm bilaterally. Eyelid creases were noted to be high in each upper eyelid. She declined surgical correction.

Epidemic keratoconjunctivitis is a highly contagious disease. The subepithelial infiltrates that develop may decrease visual acuity. Pseudomembranes of the conjunctiva may occur in severe cases and may result in permanent conjunctival scarring. Our two patients developed blepharoptosis after an adenoviral infection. On the basis of the clinical examination in two cases, and the operative findings in one case, we postulate that the mechanism of blepharoptosis is a levator attenuation/disinsertion. The marked eyelid edema associated with the viral infection may weaken the levator-tarsal attachment leading to blepharoptosis and elevation of the eyelid crease.

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Ocular Infections Secondary to Pasteurella multocida

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Pasteurella multocida is a gram-negative coccobacillus found in the normal flora of cats and dogs. Human infection secondary to P. multocida usually involves contact with animal secretions such as a bite or a lick. Pasteurella multocida has been implicated in a variety of infections, including skin, bone and joint, pulmonary, cardiovascular, and central nervous system infections. Declar infections caused by P. multocida, however, are rare. A review of the literature shows only nine cases of P. multocida ocular infections reported to date. We studied a case of orbital and periorbital cellulitis and conjunctivitis caused by P. multocida.

An 80-year-old man with a history of extracapsular cataract extraction with an intraocular lens implant in the left eye (four years previously), bilateral chronic open-angle glaucoma, and best-corrected visual acuity of R.E.: 20/70 and L.E.: 20/400 complained of pain and swelling in the left eye of 24 hours' duration, associated with copious amounts of green discharge. He denied any visual disturbance, but endstage glaucoma in the affected eye made interpretation difficult. No history of trauma to the eye was noted.

Results of physical examination disclosed a

temperature of 100.4 F with visual acuity of R.E.: 20/80+ and L.E.: counting fingers. Pinhole visual acuity of 20/70 in the right eye and 20/400 in the left eye was recorded. Intraocular pressures were R.E.: 22 mm Hg and L.E.: 35 mm Hg with a conspicuous afferent pupillary defect in the left. Extraocular movement was restricted in both lateral and downgaze on the left with 2 mm of proptosis present in the left eye. Results of external examination showed marked tense swelling of the left upper eyelid associated with copious green discharge and conjunctival hyperemia without chemosis. The cornea was clear and the anterior chamber was aphakic with no inflammation. A posterior chamber lens and capsulotomy were present. Ophthalmoscopy disclosed clear media with a cup to disk ratio of 0.8 in the right eye and 0.9 in the left eye. The remainder of the retina was normal. Enlarged, tender, left anterior cervical lymph nodes were also noted.

Laboratory studies showed a white blood cell count of 10,700/mm³ with 78% neutrophils. Gram stain of the discharge from the left eye showed many neutrophils but no organisms. Computed tomography of the head demonstrated a large soft tissue swelling in the face, extending from the malar eminence of the frontal sinus on the left. The optic nerve and extraocular muscles appeared normal. No fluid collection in the orbit was seen, and the sinuses were normal.

The patient was treated with timentin and gentamicin intravenously and gentamicin topically. *Pasteurella multocida* was grown from both a blood culture and drainage from the eye. Intravenous antibiotics given for six days were followed by amoxicillin orally for eight days. The patient was able to open his left eye on the third day of treatment. Follow-up examination showed complete resolution of the edema and full extraocular movements. Final visual acuity remained R.E.: 20/70 and L.E.: 20/400. The afferent pupillary defect resolved. On further questioning, the patient admitted having a dog at home that frequently licked the patient's hands and occasionally his face.

Human infections from *P. multocida* usually result from direct inoculation through bites, but can stem from contact with animal secretions. Ocular infections caused by *P. multocida* are extremely rare. Previously reported cases include an 11-year-old girl who suffered a cat scratch to her eye and developed endophthalmitis,³ a 44-year-old woman who developed a corneal ulcer with hypopyon after her eye was bumped by her pet dog,⁴ a 10-year-old boy

who developed endophthalmitis after a cat scratched the cornea of his eye,1 and a 51-yearold man who suffered endophthalmitis from a cat bite that penetrated his globe.2 A three-year retrospective study of infectious endophthalmitis from a tertiary referral center reported one case caused by Pasteurella species after corneal laceration by a cat. 5 Analysis of Pasteurella infections not related to animal bites shows four ocular infections during a 34-month period. These include two cases of conjunctivitis, one case each of keratitis and anterior uveitis, and one case of proptosis with pansinusitis eroding into the orbit.6 Bacteremia is an infrequent complication of Pasteurella infections, but when found, it often occurs in immunocompromised patients with cirrhosis or malignancy. Common sources of bacteremia include intra-abdominal infection, meningitis, pneumonitis, and soft tissue infections.7 Skin infections with P. multocida evoke an intense inflammatory response with much local erythema, warmth, swelling, and tenderness.

Treatment of previously reported ocular infections included medical and surgical intervention. Galloway and Robinson³ described a treatment regimen of topical and systemic antibiotics. Their patient underwent enucleation at 16 days because of continued fever. Purcell and Krachmer4 used topical therapy with preservation of the eye, but corneal scarring, cataract formation, and decreased visual acuity resulted. Weber and associates1 reported preserved vision after topical and systemic antibiotics were used. Yokoyama and associates2 used aggressive surgical management together with systemic and intravitreal antibiotics that led to a visual acuity of 40/200 in their patient. Our patient responded to intravenous and topical antibiotics.

Pasteurella multocida is susceptible to most antibiotics including penicillin G, the cephalosporins, ticarcillin, piperacillin sodium, chloramphenicol, tetracycline, and gentamicin. The antibiotic of choice is penicillin or ticarcillin. In patients allergic to penicillin, chloramphenicol or tetracycline are useful alternatives.

The unusual aspect of this case was the isolation of *P. multocida* from the blood and the discharge from the eye in the absence of an open wound. Additionally, only the eye with the intraocular lens implant was involved with infection. This case extends the spectrum of ocular infections caused by *P. multocida* to include orbital and periorbital cellulitis. Early administration of antibiotics resulted in a favor-

able outcome for our patient. Ocular infection with *P. multocida* is most likely caused by an animal scratch or lick over the eye, an event often overlooked by patients. *Pasteurella multocida* should be considered in the differential diagnosis of ocular infections and a history of contact with animals should be obtained.

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Acquired Toxoplasmic Infection as the Cause of Toxoplasmic Retinochoroiditis in Families

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The presence of active or inactive focal toxoplasmic retinochoroiditis reflects a congenital infection in essentially all cases, and occurs in the fetus only when the mother acquires active disease during pregnancy. Subsequent siblings are thought to be protected by the mother's acquired immunologic defense mechanism. Therefore, one would not expect the siblings of a child with ocular toxoplasmosis to be at risk of contracting the same ocular disease.²

Ocular toxoplamosis comprises approximately 50% of all uveitis seen in Brazil. Familial ocular toxoplasmosis is frequently observed in the southern part of Brazil (Alto Uruguai region) where the ingestion of raw pork contaminated with toxoplasmic cysts is common, which causes repeated reinfection.³

We studied the occurrence of ocular toxoplasmosis in 112 families from the city of Erexim (Rio Grande do Sul, Brazil). All patients had positive serologic findings for toxoplasmosis, a clinical picture typical of ocular toxoplasmosis with a necrotizing retinochoroiditis often associated with satellite lesions, and the exclusion of other known causes of focal retinochoroiditis, such as syphilis and tuberculosis.

Various familial patterns of ocular toxoplasmosis have been noted, including a mother and one child in nine families; a mother and two children in one family; a mother and three children in four families; a mother and four children in one family; a mother and six children in one family; and a mother and eight children in one family. Ocular toxoplasmosis was present also in two siblings of 60 families, three siblings in 18 families, four siblings in six families, five siblings in three families, and six siblings in four families. All of these families had nontwin siblings. The clinical picture typical of ocular toxoplasmosis has been seen also in three successive generations of female patients in some of the families (Fig. 1).

A large number of toxoplasma cysts have been identified in the retinas of enucleated eyes

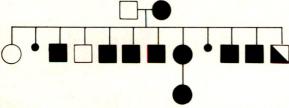


Fig. 1 (Silveira and associates). Family with ocular toxoplasmosis in the mother, seven sons, one daughter, and one granddaughter. The fully blackened symbols denote bilateral disease, while the half blackened square denotes unilateral disease.

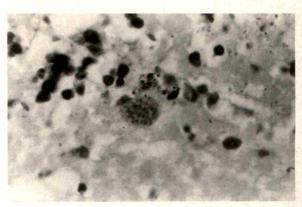


Fig. 2 (Silveira and associates). *Toxoplasma* cysts in the retina of one of two nontwin siblings who had familial ocular toxoplasmosis (hematoxylin and eosin, $\times 1,000$).

from two nontwin siblings with ocular toxoplasmosis (Fig. 2).4

The rate of miscarriage in this population is similar to that observed in other parts of Brazil. A survey of 100 children 10 to 15 years of age in a public school of Erexim showed that only two did not have serum antibodies to toxoplasmosis. Many of them also had IgM serum antibodies to the parasite, suggesting a recently acquired infection.

The evaluation of patients with acute necrotizing retinochoroiditis for circulating IgM antitoxoplasma antibodies has shown positive results in several of these patients. In other cases, patients with ocular toxoplasmosis had a past episode of systemic toxoplasmosis proven by positive IgM antibodies to the organism. In most patients, the systemic disease was relatively mild, characterized by a flu-like episode associated with lymphadenopathy.

We have examined three other families with homozygotic twins where ocular toxoplasmosis was found only in the eye of one of the twins. Serum IgG antitoxoplasma antibodies were found only in the twins with the retinal lesions.

The meaning of these observations is not totally clear. This may be a highly unusual congenital form of the disease or more likely, it is evidence of the important role of acquired *Toxoplasma* infection in the pathogenesis of this ocular disease. This latter explanation has also been suggested by Ziobrowski.⁵

We can only summarize that the incidence of acquired subclinical toxoplasmic infection that causes late, or recurrent necrotizing retinochoroiditis is probably much more frequent than previously believed.

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A Technique for Repairing Strabismus After Scleral Buckling Surgery

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Wilmer Ophthalmological Institute, the Johns Hopkins University School of Medicine. Presented in part as a poster exhibit at the annual meeting of the American Association of Pediatric Ophthalmology and Strabismus, May 18, 1988, Boston, Massachusetts.

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Repair of strabismus after scleral buckling can be difficult and unpredictable because of scar tissue and interference by the implanted material with customary surgical techniques. We describe a simplified technique for repairing strabismus after scleral buckling procedures. This technique offers advantages over previously described approaches.^{1,2}

A cul-de-sac conjunctival incision is made in the appropriate scleral quadrant in an arc, parallel to the folds of tissue in the fornix. Dissection through Tenon's capsule is carried down to the bare sclera posterior to the buckle, being careful not to disturb the fibrous capsule surrounding the exoplant. The muscle is then isolated with a muscle hook posterior to the exoplant, leaving intact the fibrous scar tissue

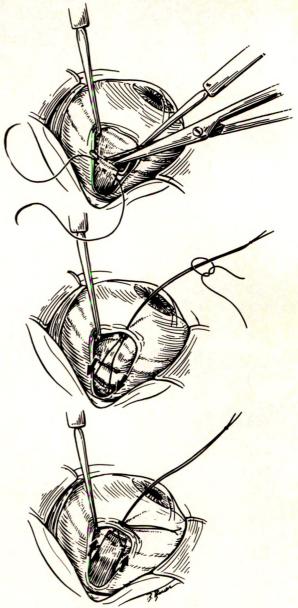


Figure (Mallette, Kwon, and Guyton). Surgical procedure, avoiding the fibrous capsule surrounding the exoplant. Top, Exposure of the "new insertion" at the posterior edge of the capsule surrounding the exoplant. A double-armed 6-0 Vicryl suture secures the muscle before tenotomy. Middle, For recession, the sutures are passed anterior to the original insertion of the muscle, and the muscle is allowed to hang back a measured amount from its original position. The sutures are brought out through the conjunctiva, and a noose is placed around them for later adjustment. Bottom, For advancement, the disinserted muscle is advanced the desired amount over the scar tissue/muscle stump. Alternatively, a straightforward resection may be done with advancement of the resected margin to the posterior edge of the buckle. In either case the sutures course forward over the old muscle stump.

covering the buckle. Conjunctiva is reflected from the scar tissue, and dissection with blunt Wescott scissors frees the muscle from any posterior scar tissue. A traction test is performed to rule out residual adhesions. That portion of the muscle entering the scar tissue surrounding the exoplant is then treated as if it were the effective insertion. A double-armed 6-0 Vicryl suture is placed, with a central knot and two marginal locking passes, and the muscle is severed from the globe at the posterior border of the capsule of the exoplant. Recession, advancement over the anterior scar tissue, or resection and advancement to the point of tenotomy may be performed (Figure). In all cases the needles are passed through the sclera at, or anterior to, the original muscle insertion, and the muscle is positioned in a hang-back fashion. Whenever possible the sutures are placed in adjustable suture fashion to allow adjustment postoperatively. Details of this adjustable suture technique have been published elsewhere.3

Previous techniques of strabismus surgery after scleral buckling procedures have involved a limbal approach and dissection of the muscle from the encapsulated exoplant. The approach through previously operated on conjunctiva and Tenon's tissue is difficult. Furthermore, dissection of the muscle from the capsule of the exoplant usually exposes the exoplant with the attendant risk of subsequent infection and extrusion. The cul-de-sac approach avoids the need to violate the fibrous capsule surrounding the exoplant, simplifies the dissection, and preserves the protective role of the capsule. Marginal myotomy has been suggested as the preferred method of weakening a muscle inserted anterior to a scleral buckle.4 Our technique is an alternative that avoids the unpredictability of marginal myotomy.

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The Treatment of an Enlarged Sarcoid Iris Nodule With Injectable Corticosteroids

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The views expressed in this article are those of the authors and do not reflect the official policy or position of the Department of the Army, Department of Defense, or the U.S. Government.

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Iris nodules occur in approximately 11% of individuals with sarcoidosis. The nodules are composed of noncaseating epithelioid cell tubercles. Although these nodules are usually small and clinically insignificant, they have been confused with iris melanomas. Massive iris nodules have been described that have filled the anterior chamber within months and led to phthisis bulbi. We successfully treated a patient with biopsy-proven sarcoidosis who had a huge, rapidly growing iris nodule with injectable corticosteroids.

A 30-year-old man with a one-year history of mild intermittent iritis came to our clinic for a follow-up examination one month after a normal eye examination. The patient had stage 2 sarcoidosis with bilateral hilar and right paratracheal adenopathy, a restrictive lung defect, and an abnormal gallium scan showing uptake in the liver, lymph nodes, and lacrimal gland. Two weeks earlier he had completed a treatment course of oral corticosteroids for his pulmonary condition. This treatment consisted of an initial dose of 80 mg of prednisolone which had been decreased gradually over a four-month period.

Results of ocular examination showed a visual acuity of R.E.: 20/25 and L.E.: 20/20. Fine keratic precipitates were noted on the right corneal endothelium, as were 1+ cells in the right anterior chamber, and an inferior $1\times$

2-mm flesh-colored iris nodule temporally near the periphery of the iris. The patient was treated with 1% prednisolone acetate eyedrops every six hours, which he used regularly for the next several months. The patient was lost to adequate follow-up until approximately six months later. At this time his visual acuity in the right eye had decreased to 20/60 and the iris nodule had increased in size and completely filled the angle at the iris root from the 3:30 to the 7:30 o'clock meridian. This bulky mass touched the corneal endothelium inferiorly, nearly reached the pupil centrally, and produced a peripheral sector cortical cataract beneath the lesion (Fig. 1). Posterior synechiae were noted at the pupillary margin from the 4 to the 7 o'clock meridian. The remainder of the anterior chamber was deep with Grade 4 open angles, a normal B-scan posterior to the iris, and normal intraocular pressures. The right fundus was normal. Results of the examination of the left eve were normal.

To avoid further systemic corticosteroids the patient was treated with 20 mg of betamethasone injected subconjunctivally into the conjunctival cul-de-sac radial to the lesion. The nodule began to regress within two weeks, at which time a second injection was given. Three months after treatment, visual acuity was 20/20 with a clear cornea. The sector cataract remained and anterior synechiae fixed the peripheral iris to the border of the clear cornea from the 4 to the 7:30 o'clock meridian. From

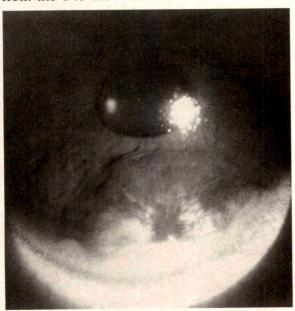


Fig. 1 (Mader, Chismire, and Cornell). The iris nodule after an increase in size. The peripheral sector cortical cataract is obscured by the lesion.

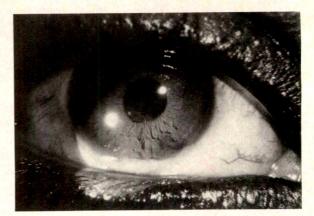


Fig. 2 (Mader, Chismire, and Cornell). Three months after treatment the mass had resolved, but posterior synechiae are evident.

this synechial attachment the iris stretched tautly to the pupillary border where posterior synechiae further adhered the iris to the lens (Fig. 2). Approximately three months after the injection, the patient was noted to have a testicular mass. Biopsy of the mass showed a noncaseating granuloma, which was consistent with the diagnosis of sarcoidosis.

This case graphically illustrates the sensitivity of a large sarcoid iris nodule to corticosteroid injection. If the growth of such rapidly enlarging iris nodules is not promptly checked the results can be devastating. Usually, high-dose systemic corticosteroids are recommended for the treatment of advanced anterior segment inflammation. We believe these lesions may be treated with injectable subconjunctival corticosteroids. This treatment is effective and avoids the complications associated with high-dose systemic corticosteroids.

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Teflon Sleeve Canalicular Splints

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Canalicular lacerations are repaired routinely with the aid of internal splinting devices such as a metal canalicular rod, silicone stents, or continuous loop silicone tubes. Each of these devices is effective in preserving the patency of the canaliculus during the healing period. While these devices are available in most ophthalmic operating rooms, they are rarely available in emergency and general operating rooms. When these specialized devices were unavailable, we used the outer Teflon sleeve of an intravenous catheter (Fig. 1) as a temporary splint for canalicular repair.

This Teflon sleeve is available in almost all emergency and operating rooms. The sleeve is inexpensive, it comes in a sterile package and in varying sizes. It has a tapered end and is sufficiently rigid to permit easy threading into the severed canaliculus. The distal end of the Teflon tube can be cut to the desired length and then sutured to the eyelid margin to prevent migration (Fig. 2). The Teflon is well tolerated by the local tissues and is sufficiently flexible to be comfortable to the patient. Direct irrigation of the lacrimal system may be carried out through the lumen of the tube.

To date, we have successfully used this simple device as a temporary splint in three patients. In each case, the Teflon sleeve was

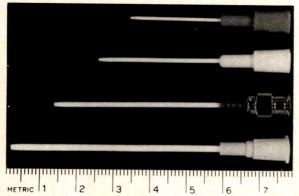


Fig. 1 (Haik). Intravenous Teflon sleeves of varying lengths and diameters. Bottom to top, 16, 18, 20, and 22 gauge.

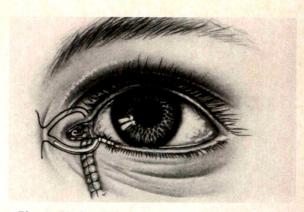


Fig. 2 (Haik). Teflon sleeve used as a temporary canalicular splint during repair of a lower eyelid laceration.

subsequently replaced within one week by continuous loop silicone tubing.

New Lens System for Indirect Fundus Biomicroscopy

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The hand-held +90-diopter indirect double aspheric biomicroscopy lens has become a common tool for examination of the vitreous and ocular fundus. This lens offers the advantage of noncontact examination and a large field of vision, even when there is a relatively small pupil. 1,2 Unfortunately, reduced depth perception limits the use of this lens to cases where assessment of three-dimensional details is not required. The axial magnification (axial magnification = lateral magnification²)³ obtained with the +90-diopter lens is 42.44% of the original image size (the lateral magnification with the +90-diopter lens is 65% for an emmetropic 59-diopter eye). Therefore, the lens is not useful for detecting retinal thickening, such as macular edema, or for detecting small elevations of the retinal pigment epithelium or neurosensory retina, such as choroidal neovascularization or central serous chorioretinopathy. The reduced depth perception obtained with this lens and its inability to keep the eye open



Fig. 1 (Bartov and Lewis). A +90-diopter lens and -64.5-diopter plano-concave contact lens held together by Millipore tape.

also prevents using it in the treatment of macular diseases.

Thus, in cases where a three-dimensional view is needed, or when treating macular diseases, the use of a plano-concave contact lens is still required since it preserves the 1:1 relationship between fundus detail and size of the observed image. It also prevents the eye from blinking. The major optical disadvantage of a contact lens, however, is the limitation on the observed field of view, which is determined by the size of the pupil.

We found a simple way to perform diagnostic biomicroscopy and laser photocoagulation while obtaining both a large field and threedimensional viewing. This is accomplished by using both the contact lens and the +90-diopter lens in a piggyback fashion (Fig. 1). When a thin plano-convex contact lens is placed on the cornea and a +90-diopter lens is held toward the examiner 10 mm from the contact lens surface, an optical system with approximately +60 diopters of power is obtained. This increases the field of view and offers a 1:1 size relationship between the retina and the image. A +60diopter indirect aspheric lens will provide the same advantages. In contrast to a +60-diopter indirect lens, 4,5 however, the contact lens of our system also keeps the eye open and prevents blinking, which could interfere with laser photocoagulation.

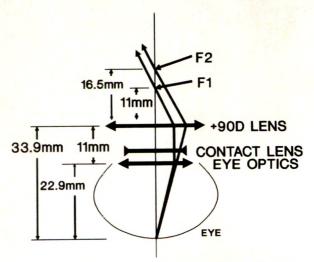


Fig. 2 (Bartov and Lewis). Optical relationship between an emmetropic eye, +90-diopter lens, and -64.5-diopter plano-concave contact lens.

The +90-diopter lens is attached to the flange of a contact lens by a Millipore filter (Fig. 1). We used a contact lens of -64.5 diopters, but any thin plano-concave contact lens with a distance between the contact surface and the edge of the holding flange of 10 to 12 mm will do just as well.

Figure 2 demonstrates the optical relationship between the various elements of this system. F1 is the point at which the retinal image will be focused using a +90-diopter lens alone. The point where the image of the retina will be focused after a contact lens has neutralized the refracting power of the eye is 34 mm or -29 diopters from the +90-diopter lens. The focal distance of F2 is obtained by adding -29 diopters to +90 diopters (+61 diopters, comparable to the refractive power of the emmetropic eye) and is equivalent to 16.5, mm. Therefore, there is practically no minification effect, neither in the lateral nor in the axial planes. One should keep in mind that the image is inverted.

We have found that the combined use of these two popular lenses is even more gratifying than using each alone.

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Correspondence

Correspondence concerning recent articles or other material published in The Journal should be submitted within six weeks of publication. Correspondence must be typed double-spaced, on 8½ × 11-inch bond paper with 1½-inch margins on all four sides and should be no more than two typewritten pages in length.

Every effort will be made to resolve controversies between the correspondents and the authors of the article before

publication.

Monocular Diplopia Accompanying Ordinary Refractive Errors

EDITOR:

In the article "Monocular diplopia accompanying ordinary refractive errors" by P. Coffeen and D. L. Guyton (Am. J. Ophthalmol. 105:451), May 1988), the authors conclude that in the setting of ordinary refractive errors, monocular diplopia is secondary to optical irregularity. I have experienced transient monocular diplopia caused by a mapdot-fingerprint dystrophy. The monocular diplopia was often present in the morning and would clear up within an hour. The diplopia disappeared with a pinhole and could be corrected with a cyclinder. Although this condition had been present for the past 15 years, it disappeared after one episode of spontaneous epithelial erosion and healing.

> LOUIS J. GIRARD, M.D. Houston, Texas

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EDITOR:

We thank Dr. Girard for his observation. Map-dot-fingerprint dystrophy of the cornea is a known cause of monocular diplopia, and was reviewed most recently by Hirst, Miller, and Johnson. That Dr. Girard could correct his monocular diplopia with a cylindrical lens supports our thesis that ordinary, regular refractive errors can accentuate the effects of minor optical irregularities in the production of monocular diplopia. Correction of such refractive errors can often minimize or eliminate the monocular diplopia, even though the minor optical irregularities are still present.

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A Double-Masked Study of Timolol and Pilocarpine Combined

EDITOR:

In the article "A double-masked study of timolol and pilocarpine combined" by P. J. Airaksinen, R. Valkonen, T. Stenborg, K. Takki, A. Klemetti, M. Kontkanen, and P. Oskala (Am. J. Ophthalmol. 104:587, December 1987), the authors compared the effect of timolol and pilocarpine combined, administered only twice daily, to pilocarpine administered four times daily. They concluded that the drug combination "lowered intraocular pressure at least as effectively as, if not more effectively than, pilocarpine administered four times a day." We believe that the design of the study and the results do not lead to this conclusion. The combined preparation was not compared with timolol alone and therefore the effectiveness of the combination could very well be caused by the timolol only. On examination 1 (12 hours after the last instillation of drops) the reduction of intraocular pressure by the combined preparation is probably not caused by the additive effect of the two drugs, as claimed by the authors. Because pilocarpine is effective only six to eight hours, the hypotensive effect is caused by the long-acting timolol only.

There is no doubt that a combined preparation of timolol and pilocarpine may improve compliance. However, in order to prove its efficacy, it should be compared not only to pilocarpine alone but also to timolol alone.

ORNA GEYER, M.D. MOSHE LAZAR, M.D. Tel Aviv, Israel

Reply

EDITOR:

In our study, the intraocular pressure measurements of the patients receiving the timolol-pilocarpine combination drug twice a day were lower than the intraocular pressure measurements of the group receiving pilocarpine alone four times a day. Therefore, the combination drug was more effective in lowering intraocular pressure than pilocarpine alone.

Doctors Geyer and Lazar point out that this new combination drug should also be compared to timolol alone. Results of such a study have been reported recently by Høvding and Aasved.¹ They found that the timolol-pilocarpine combination drug administered twice a day regulated intraocular pressure better than timolol eyedrops alone. Additionally, their results showed that the additional effect of pilocarpine was detectable 12 hours after drop administration.

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Reference

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Irregular Pupil Cycling as a Characteristic Abnormality in Patients With Demyelinative Optic Neuropathy

EDITOR:

In the article "Irregular pupil cycling as a characteristic abnormality in patients with demyelinative optic neuropathy" by J. G. Milton, A. Longtin, T. H. Kirkham, and G. S. Francis (Am. J. Ophthalmol. 105:402, April 1988), the authors used a highly sophisticated method to point out that irregular pupil cycling is specific in demyelinative disease. They state that this phenomenon is not caused by fatigue-like visual characteristics, but caused by prolonged latency of the pupillary reflex concerned with transmission prolongation in demyelinated fibers. They listed two reasons: the absence of progressive diminution, and the different time course with pupillary fatigue.

In general, the output signal of the negative feedback system will oscillate when the feedback gain is too high. Pupillary oscillation induced by artificial increase of the system gain is one example. The oscillation occurs with the frequency where the transfer function of the system shows 180-degree phase lag. If the gain at this frequency is greater than unity, oscillation continues. Transmission prolongation of the system enlarges phase lag and then reduces the oscillation frequency. However, at the lower frequency, the pupillary gain is higher in this frequency region. This means that the delay of transmission cannot disturb the continuous oscillation. Only abnormal reduction of the gain causes cessation of the cycling. Progressive gain reduction can be called a "fatigue-like phenomenon," whereas the gain reduction itself may be involved with difficulties of transmitting higher firing rates (unpublished data).

I studied artificial control of feedback gain of the pupillary system using a method similar to that of the authors. The stimulus intensity, however, was continuously changing proportional to the reciprocal of the pupillary area, and the area of the pupil was measured with a silicon vidicon. The vidicon had an afterimage and then increased the latency of the feedback loop. In normal subjects, regular cycling could be obtained up to 0.7 Hz.

While the feedback technique may detect response delay, in order to measure progressive gain decrease, one need not apply feed-

back technique. The abnormal pupillary escape induced by relatively intense light and visual fatigue correlates well in optic neuritis.1 Both phenomena are especially large in demyelinated disease. The recordings show that the abnormal pupillary escape started just after the onset of the stimulus and became stable within two minutes. In severe cases the pupil could hold constriction only a few seconds. Sometimes, sudden recovery of pupillary reaction was observed during the escape. This time course and frequency of sudden recovery also varied with the stimulus intensity. The discussion by the authors may be misleading if viewed from these characteristics. It should be added that abnormal escape may consist of a different mechanism than that of normal pupillary escape.

KAZUHIKO UKAI, Ph.D. Kanagawa, Japan

Reply

EDITOR.

We thank Dr. Ukai for his comments. The first issue raised by Dr. Ukai concerns whether a prolonged latency time could cause pupil cycling to stop. We agree that simply increasing the latency time would not cause the cycling to stop. We proposed a different mechanism. In a partially demyelinated nerve there will be a greater distribution of conduction velocities than in normally myelinated fibers. Additionally, some of the demyelinated nerve fibers will intermittently block the conduction of repetitive impulses. We suggested that these two phenomena may sufficiently desynchronize the afferent nerve impulse train to the point that the midbrain nuclei fail to respond correctly. In simpler terms, the cycling becomes irregular or stops because the wire has been intermittently cut.

The second issue raised by Dr. Ukai concerns whether changes in gain could underlie these irregularities in pupil cycling. In our experiment the gain was composed of two parts: (1) the intrinsic gain of the pupil light reflex pathways, $G_{\rm in}$; and (2) the external gain of the "area comparator," $G_{\rm ext}$. The area comparator we used is piecewise constant negative feedback: the light is on or off depending on whether pupil area is, respectively, greater than or less than an adjustable area threshold, θ . $G_{\rm ext} = 0$ for all values of pupil area except at the area threshold where $G_{\rm ext}$ is infi-

nite. Provided that there is a pupillary response to the light pulse, the condition for pupil cycling is that θ be less than the maximum pupil area during cycling (Figure 1 in our article). This criterion for cycling is different from the Nyquist criterion cited by Dr. Ukai because our experimental conditions are different from those he is considering.

The role of changes in G_{in} on pupil cycling follows. Changes in G_{in} will affect the minimum and maximum pupil areas during cycling. If these changes in G_{in} are large enough such that the minimum pupil area becomes larger than θ , then cycling stops. This might occur, for example, because of pupillary escape. However, as we pointed out, we were unable to restart pupil cycling by increasing θ .

The final issue raised by Dr. Ukai concerns pupillary escape. Certainly the experimental conditions used in his work¹ (10-second pulses of "intense" light) are different from those in our experiment (≤0.5 second pulses of "not very intense" light). Dr. Ukai may be correct in suggesting that abnormal escape occurs, but we do not know to what mechanisms he is referring.

JOHN G. MILTON, M.D. ANDRÉ LONGTIN, M.Sc. TREVOR H. KIRKHAM, M.D. GORDON S. FRANCIS, M.D. Montreal, Canada

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The Diagnosis and Treatment of Bilateral Masked Superior Oblique Palsy

EDITOR:

In the article "The diagnosis and treatment of bilateral masked superior oblique palsy" by B. J. Kushner (Am. J. Ophthalmol. 105:186, February 1988), the author proposed to explain why the signs of less affected muscle are masked in asymmetric bilateral superior oblique muscle palsy. His rationale was based on measurements of the ocular deviation in

different positions, using prism and cover testing. He based his explanation for the absent or decreased hypertropia of the eye with the less affected muscle when the head is tilted to its side (Bielschowsky's sign) on the inhibition of the innervation to the ipsilateral superior rectus muscle when this eye is fixing. If this were the only determinant factor, however, there would be inconcomitance in the cover test. When the less affected eye is covered, the increased innervation to the depressor muscles of this eye (inferior rectus and superior oblique) would disappear, which would then cause Bielschowsky's sign to develop further. But this does not occur. When the less affected eye is covered, it does not elevate, despite the stimulation of the superior rectus muscle by the vestibular mechanism induced by the head tilting to the side because of the increased innervation to the depressor muscles, caused by an increased innervation to the depressor muscles of the fellow fixing eye (Hering's law of equal innervation). The increased innervation to the depressor muscles of this eye (the one that has the more affected superior oblique muscle) is caused by the weakness of one of the depressor muscles and the consequent contracture of the ipsilateral superior rectus muscle.1-3

These two factors also explain the smaller differences in hypertropia between right and left head tilt in patients with bilateral superior oblique palsy than in patients with unilateral superior oblique palsy in that the elevation of the more affected eye is also reduced when the head is tilted to its side.

With regard to the absence or reduction of the inferior oblique overaction in the less affected eye, and the consequent absence or reduction of the inversion of the hypertropia in the supra-adduction position, it can be explained in the same manner. When the inferior oblique action of the less affected eye is evaluated, the more involved eye is forced to fixate in the supra-abduction position (position of maximal stimulation of the superior rectus muscle). The superior rectus muscle of the more affected eye is overacting. An overacting ocular muscle requires less innervation to accomplish a certain movement. As the fixing eye determines the neural input to the nonfixing eye, the inferior oblique muscle of the nonfixing eye receives less innervation, which compensates its tendency to overact. The same phenomenon can be observed in

essential strabismus with inferior oblique muscle overaction; if the eye with the overacting inferior oblique muscle fixates in the supra-adduction position, the other eye will show a hypotropia. As the inferior oblique muscle of the fixing eye requires less innervation to place the eye in this position, the superior rectus muscle of the fellow eye also receives decreased innervation.

When the less affected eye is in the infraadduction position, the contracture of the superior rectus muscle of the more affected eye (the fixing eye) causes a limitation of depression. This causes an increased innervation to the ipsilateral inferior rectus muscle and consequently, an increased innervation to the less affected eye's superior oblique muscle, thereby masking its underaction.

I believe that both my explanation and Dr. Kushner's are not mutually exclusive.

CARLOS SOUZA-DIAS, M.D. São Paulo, Brazil

References

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- 2. ——: Surgical management of superior oblique paresis. In Moore, S., Mein, J., and Stockbridge, L. (eds.): Orthoptics. Past, Present, and Future. Miami, Symposia Specialists, 1976, pp. 379–391.
- 3. Prieto-Diaz, J., and Souza-Dias, C.: Estrabismo. São Paulo, Roca Ed., 1986, pp. 297–301.

Reply _

EDITOR:

Dr. Souza-Dias raises two issues regarding my explanation as to why the palsy of the lesser affected eye in patients with bilateral superior oblique palsy may be masked.

First, he believes that my discussion does not explain the absence of a hypertropia of the lesser affected eye on forced head tilt when the more affected eye is fixing. Because patients with bilateral masked superior oblique palsy typically fixate with the lesser affected eye, I limited my discussion to the mechanism of masking when the lesser affected eye was fixing. When the less affected eye is covered, the more affected eye picks up fixation. This results in increased innervation

to the depressor muscles of that eye, which also causes increased innervation to the depressor muscles of the less affected eye (Hering's law). This results in an inhibition of the superior rectus muscle in the less affected eye (Sherrington's law), which negates the increased stimulation to the superior rectus muscle because of the forced head tilt. This is similar to the explanation outlined by Dr. Souza-Dias and I agree with him, but with one exception. He suggests that contracture of the superior rectus muscle of the more affected eye is part of this explanation. I believe that the mechanism I have outlined is not contingent upon contracture of the superior rectus muscle in the more affected eye.

Secondly, Dr. Souza-Dias believes that his and my explanations of the bilateral masking of superior oblique palsy are not mutually exclusive. Although I agree, I do not think that mechanical contracture of the superior rectus muscle of the more affected eye is an essential ingredient. I have examined a patient with what was later proven to be a traumatic bilateral masked superior oblique palsy within 24 hours after head injury. At that time the palsy of the less affected eye was totally masked. Certainly, there was no time for contracture to occur. Of the nine patients I described, only two of them had clinically detectable contracture of the superior rectus muscles in the more affected eye, as tested with intraoperative forced duction testing.

Although I do not believe the presence of contracture of the superior rectus muscle of the more affected eye is an essential ingredient, the explanation offered by Dr. Souza-Dias works nicely with the one that I hypothesized.

BURTON J. KUSHNER, M.D. Madison, Wisconsin

Enlargement of the Blind Spot Caused by Papilledema

EDITOR:

We would like to add some information to the article "Enlargement of the blind spot caused by papilledema," by J. J. Corbett, D. M. Jacobson, R. C. Mauer, and H. S. Thompson (Am. J. Ophthalmol. 105:261, March 1988). The reduction in size of the blind spot in cases of papilledema by using progressively stronger plus lenses during perimetry is not unknown to us in Holland. The same principle may be used to reduce the field defects in many other elevations of the retina, specifically in cases of choroidal tumors such as melanomas or choroidal metastases.

One of us (J.J.v.E.) has developed a similar technique to map visual fields in patients with severe myopia. Many of these patients have a nasal fundus ectasia, which causes a relative temporal scotoma to appear on perimetry. Such a scotoma should be demonstrable theoretically on perimetry by adding minus lenses in front of the eye being examined. Such a superimposition of minus lenses is often ineffective, however, as it is simply overcompensated by the patient's accommodation. Therefore we have been using a series of minus lenses from a trial set with 5-mm holes drilled through the centers. These lenses are superimposed over the patient's normal correction and the visual fields are plotted through progressively more minus holed lenses. The hole allows the patient to maintain central fixation while the peripheral retina is subjected to the higher minus power of the holed lens.

With this technique one can determine whether degenerative changes have already taken place in a nasal staphyloma. That is, it is often possible to obtain a normal visual field in a young patient with progressive myopia whereas in a patient in whom degenerative changes have already taken place, the relative field defect over the area of the staphyloma is not completely reduceable. This technique also enables one to differentiate between field loss resulting from myopia as opposed to field loss resulting from a possible chiasmal tumor.

J. J. VAN ENDT, M.D. H. A. WESSELS, M.D. Roosendaal, The Netherlands

BOOK REVIEWS

Edited by H. Stanley Thompson, M.D.

Computed Tomography of the Temporal Bone and Orbit. By Frans W. Zonneveld. Baltimore, Urban & Schwarzenberg, 1987. 205 pages, index, illustrated. \$110

Reviewed by Jeffrey A. Nerad and Keith D. Carter Iowa City, Iowa

Dr. Zonneveld has combined the knowledge of various authorities in the fields of radiology, anatomy, otorhinolaryngology, ophthalmology, and plastic surgery to correlate diagnostic images with clinical pathology. The emphasis of this book is on high-resolution computed

tomography.

Three chapters cover the technical aspects of computed tomography and cryosectioning. Principles of computed tomography, the evolution of scanners, and their capacities in diagnostic imaging are discussed. Two chapters are devoted to the diagnostic imaging of the temporal bone and its clinical applications. These chapters are of limited interest to the ophthalmologist. The rest of the book is devoted to computed tomography imaging of the orbit. Patient positioning and scanning planes are discussed in detail. The correlative anatomy is superb. A nomenclature table that serves as a guide for the correlative computed tomography image and cryosectioned anatomy is located at the end of the book.

The author has done a great deal. He has made frozen cadaver head slices at the same plane as the computed tomographic sections. These slices of tissue have been photographed and arranged beside the computed tomographic image so that comparisons can be made. This technique, euphemistically called "cryosection of correlative anatomy," is a useful way to learn how to make sense out of computed tomography images. This book is not a clinician's guide to the diagnosis of orbital diseases, but is a good anatomic monograph. It is recommended as a reference work for the clinician with an interest in computed tomography imaging.

Headache, ed. 2. By Neil Hugh Raskin. New York, Churchill Livingstone Inc., 1988. 396 pages, index, illustrated. \$49

Reviewed by James J. Corbett Iowa City, Iowa

The first edition of this book was published in 1980 and it has become the best single volume available on headaches. Now Dr. Raskin has done a major revision and update of his book. Of the 11 chapters, four are of special interest to ophthalmologists. The chapter on the clinical aspects of migraine includes details on the visual prodrome of migraine, on ophthalmoplegic migraine, on "ice pick" pains, and on late life migrainous accompaniments. Chapters of special ophthalmic interest focus on cluster headache, on giant cell arteritis, and on facial pain. Dr. Raskin's book is abundantly referenced. In the chapter on migraine treatment alone there are 420 references of which 30% are from 1984 or later. This is a superb, readable, and clinically useful source book on the subject of headache. It is the most authoritative, and the most affordable source of detailed information obtainable on this common problem. I strongly recommend it to the practicing ophthalmologist and to anyone who regularly sees patients with headache.

Books Received

Cataracts. Transactions of the New Orleans Academy of Ophthalmology. Edited by Delmar R. Caldwell. New York, Raven Press, 1988. 379 pages, index, illustrated. \$110

This volume is a record of the 36th annual session of the New Orleans Academy of Ophthalmology, held in February 1987.

Obituary

DAVID M. WORTHEN 1936-1988

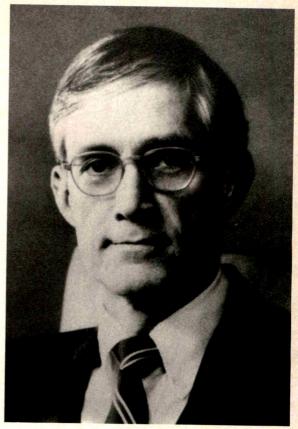
David McQuarrie Worthen, until recently Assistant Chief Medical Director for Academic Affairs for the Veterans Administration, died at his home in Potomac, Maryland of amyotrophic lateral sclerosis on April 14, 1988, one month before his 52nd birthday. When he retired because of medical disability in 1987 he was a member of the faculties of the medical schools at Georgetown, Howard, and Johns Hopkins universities.

A native of Provo, Utah, he attended the University of Utah through two years of medical school. He played several musical instruments and was a professional percussionist at age 15, supporting himself through college and medical school by playing drums and piano. This talent led to a crisis; he auditioned for a position with the Woody Herman Band, reaching the semifinals. Fortunately for ophthalmology the other drummer was offered the job. He graduated from medical school at the University of Minnesota, where he became a member of Alpha Omega Alpha.

Worthen and his wife, Gaye, met when they were students at the University of Utah and were married during medical school years. He interned at the U.S. Navy Hospital in Oakland, California. While in the Navy, he had an intensive course in psychiatry and served two years as a staff psychiatrist before entering an ophthalmology residency in 1964 at the Massachusetts Eye and Ear Infirmary. While residents, he and Richard Brubaker developed a small, inexpensive instrument for cryoextraction of the lens that was widely used for several years.

He remained in Boston until 1970 in a group practice, serving on the faculty of the Howe Laboratory and as a consultant at Peter Bent Brigham and Childrens Hospitals. He became skilled in electron microscopy and did pioneering studies of the anterior segment in glaucoma.

In 1970, he joined the faculty of the Department of Ophthalmology at the University of Florida in Gainesville. He became Chief of the Ophthalmology Service at the Gainesville Veterans Administration Hospital. In addition to teaching, medical care, research, and administration, he completed a Master of Arts Degree in Education at the University of Florida.



David M. Worthen, 1936-1988

In 1974, he was named head of the ophthal-mology program at the University of California in San Diego and became Chief of Ophthalmology at the San Diego Veterans Administration Medical Center. He was named an Associate Examiner for the American Board of Ophthalmology, and assumed responsibility for ophthalmic basic science teaching in several ongoing courses. In 1977, he became Associate Secretary for Continuing Education of the American Academy of Ophthalmology.

Under his direction the section of ophthal-mology at the University of California expanded. His research interests broadened to include the biochemical function of the trabecular meshwork and he continued clinical studies, started in Florida, on laser treatment for openangle glaucoma. With M. Gary Wickham, he performed the first systematic studies of argon laser trabeculoplasty in the United States. The method they devised is the forerunner of the one used today.

Worthen became interested in clinical trials and developed a plan for a multicenter trial to clarify the efficacy and safety of argon laser trabeculoplasty. This study was funded in 1980, but was not implemented because, in that year, he moved to Washington to the central office of the Veterans Administration. His study plan was used in developing the plan for the Glaucoma Laser Trial, an ongoing clinical trial.

At the Veterans Administration central office he headed the largest coordinated health care education program in the nation. He managed nearly 1,000 cooperative training agreements between the Veterans Administration and schools of medicine, dentistry, nursing, pharmacy, social work, and other associated health professions. He was responsible for continuing education of health professionals and other staff at the 172 Veterans Administration Medical Centers.

In 1975, he joined the Ophthalmic Devices Panel of the Food and Drug Administration, which he chaired from 1977 through 1982. He served as a consultant to the panel until 1987. During hearings his gentle, thoughtful guidance was much appreciated by panel members and applicants. He served on 16 other advisory groups on medical education, government regulation, health, and fitness. His contributions have been recognized by commendations from the American Academy of Ophthalmology, the Food and Drug Administration commissioner, the chief medical director of the Veterans Administration, the Surgeon General, Congress, and the President of the United States. At his retirement, the Veterans Administration established the David M. Worthen Award for Academic Excellence. At Georgetown University his contributions have been commemorated by creation of the David M. Worthen Center for Clinical Studies. At the Wilmer Ophthalmologic Institute, a named lectureship and fellowship has been established.

David Worthen believed it important for each person to strive to do his best. This is reflected in his work and his commitment to physical fitness. He was a world class long-distance runner, completing the Boston Marathon 19 times, in addition to many other marathon and longer distance races. His best time in the Boston Marathon was two hours 34 minutes, of which he was rightfully proud. He was a National Doctors' Marathon Champion for the 50-mile race in 1980.

He continued as a teacher after his career was shortened by illness. He wrote he was glad to learn his fatal illness would not affect his mental capacity. He sought to clarify the effects of his illness, and urged his family and peers to go on productively in the face of adversity. His article concerning the physician ill with a fatal disease has been widely reprinted (Worthen, D. M.: Inside the diagnosis. JAMA 258:1255, 1987).

David Worthen has been important to his wife and five children, his peers, ophthalmology, staff of the Veterans Administration, many with regulatory responsibilities, and patients. We shall miss him.

DOUGLAS E. GAASTERLAND and GAYE B. WORTHEN

ABSTRACT DEPARTMENT

Edited by David Shoch, M.D.

Acta Pediatrica Scandinavica

Neonatal chlamydial conjunctivitis. Sandstrom, I., Kallings, I., and Melen, B. (Dept. Ophthalmol., Sodersjukhuset, S-10064 Stockholm, Sweden). Acta Pediatr. Scand. 77:207, 1988.

In 160 infants with neonatal conjunctivitis, 33 of the infections were caused by Chlamydia trachomatis. Approximately 60% of the affected infants also had infections of the nasopharynx. All the infants were treated with oral erythromycin, 25 mg/kg of body weight, every 12 hours for 14 days. All were clinically cured but one infant had a persistent asymptomatic chlamydial ocular infection. While infants with chlamydial infections had substantially higher levels of IgG antibodies than did control infants, this may not be diagnostic since the IgG antibodies may be obtained from the mother. Detection of specific IgM may be of diagnostic value. (3 figures, 3 tables, 20 references)— David Shoch

American Journal of Medical Genetics

Optic nerve coloboma associated with renal disease. Weaver, R. G., Cashwell, L. F., Lorentz, W., Whiteman, D., Geisinger, K. R. and Ball, M. (Dept. Ophthalmol., Wake Forest Univ., 300 S. Hawthorne Rd., Winston-Salem, NC 27103). Am. J. Med. Genet. 29:597, 1988.

Two brothers with similar optic nerve colobomas had renal interstitial fibrosis. In one brother the interstitial fibrosis was associated with tubular atrophy and renal failure. The authors were unable to identify a chromosomal abnormality as the cause of this association. Since this entity occurred in two brothers with no other affected family members the inheritance pattern may be either autosomal recessive or X-linked recessive. This association of cavitary optic disk anomaly and renal failure may represent a new syndrome. (6 figures, 16 references)—David Shoch

British Journal of Ophthalmology

Fluorescein angiography of anterior uveal melanocytic tumours. Dart, J. K., Marsh, R. J., Garner, A., and Cooling, R. J. (Dept. Clin. Ophthalmol., Moorfields Eye Hosp., City Road, London EC1V 2PD, England). Br. J. Ophthalmol. 72:326, 1988.

The authors studied 32 cases of melanocytic tumors of the anterior uvea. Fourteen of the cases were categorized histologically. An additional eight cases did not have histologic diagnosis but were considered benign because they had undergone no change with a minimum four year follow-up. All patients underwent iris angiography and the following differentiating characteristics were found to be statistically significant: very small tumors were more likely to be benign (P = .029); glaucoma and episcleral vascular dilatation occurred only with ciliary body tumors; if the tumor involved the anterior chamber angle it was likely to be malignant (P=.019); and if the fluorescein angiogram showed a disorganized vasculature and gross late leakage there was a 50% probability that the lesion was malignant and about a 33% possibility that the cytologic findings were equivocal. Complete masking of fluorescence occurred in four of nine benign tumors, but no malignant tumors showed this characteristic. Early leakage of dye was not specific to any tumor category. (8 figures, 6 tables, 10 references)—David Shoch

Treatment of senile entropion with botulinum toxin. Clarke, J. R., and Spalton, D. J. (Med. Eye Unit, St. Thomas's Hosp., London SE1 7EH, England). Br. J. Ophthalmol. 72:361, 1988.

The authors injected botulinum toxin into the preseptal orbicularis muscle of the lower eyelids in 12 patients with spasm of the marginal musculature and spastic entropion. Ten of the patients had marked relief of symptoms for an average of 14.8 weeks. Botulinum toxin is suggested for those patients with spastic entropion

in whom surgery is not possible. (9 references)

—David Shoch

British Journal of Radiology

Increased risk of cataract in patients receiving radiotherapy to the eye: a pilot study. Dean, G., Alderson, M., and Maximilien, R. (73 Lower Baggot St., Dublin 2, Ireland). Br. J. Radiol. 61:309, 1988.

The authors traced 507 persons who had previously undergone radiotherapy to the face, primarily for dermatologic conditions. The patients had been treated with superficial x-rays in the range of 60 to 150 kV. Information suitable for analysis was available on 165 persons, of whom 23 had developed other ocular diseases that prevented examination of the lens. Of the remaining 142 patients, 32 had cataracts and one had a probable cataract. Nineteen patients had undergone cataract surgery. In a study of 142 matched control patients, four had undergone cataract surgery. Therefore, the risk of cataracts for those receiving radiation to the face is five times greater than that in a control population not exposed to radiotherapy. (3 tables, 5 references)—David Shoch

Experimental Eye Research

Corneal transmission in whole human eyes. Van Best, J. A., Bollenmeijer, J. G., and Sterk, C. C. (Dept. Ophthalmol., Leiden Univ. Hosp., Bijnsburgerweg 10, 2333 AA Leiden, The Netherlands). Exp. Eye Res. 46:765, 1988.

Some investigators have questioned whether fluorescein angiography might be subject to error because of loss of both excitation and fluorescent light as a result of absorption and scatter in the cornea. The authors measured the transmission of blue-green argon laser light at wavelengths of 488 and 514.5 nm through clear, healthy corneas by implanting a photodiode in whole human donor eyes that had been enucleated from 3.5 to 16 hours before measurement. The mean corneal transmission in seven eyes, with a donor age ranging from 32 to 84 years, was $93.2\% \pm 3.2\%$. Thus, little correction is necessary for light loss in healthy corneas. (1 figure, 1 table, 9 references)-David Shoch

Eye

Surgical management of ocular hypotony.

Demeler, U. (Eye Dept., Univ. Bremen, Bremen,
W. Germany). Eye 2:77, 1988.

Ten eyes were hypotonous because of trauma and three as a result of antiglaucoma surgery. To correct the hypotony, the authors made a partial thickness scleral flap 3 to 4 mm from the corneoscleral limbus and then incised the sclera 1 to 2 mm from the corneoscleral limbus. The ciliary muscle was then directly sutured to the anterior lip of the sclera at the scleral spur, which effectively closed the cleft. The ten eyes that were hypotonous as a result of trauma responded successfully to this surgical intervention. Increased intraocular pressure recurred in the three eyes that had hypotony as a procedures. of antiglaucoma references)—David Shoch

Huematic. An automated scorer for the Farnsworth-Munsell 100-Hue test. Hill, A. R., Reeves, B. C., and Burgess, A. (Visual Sci. Unit, Radcliffe Infirm., Woodstock Rd., Oxford OX2 6HE, England). Eye 2:80, 1988.

The automatic scorer (Heumatic) consists of a series of codes on the bottom of the caps. A standard light pen identifies the bar codes and a microcomputer analyzes and prints the results. The printout includes patient details, errors by cap position, and peak error positions for congenital color vision deficiency. The program analyzes the total error score as contrasted to established norms. The results are available within four minutes of completing the test procedure. (4 figures, 14 references)—David Shoch

Histological changes in congenital and acquired blepharoptosis. Sutula, F. C. (3 Hawthorne Pl., #106, Boston, MA 02114). Eye 2:179, 1988.

Histologic examination of eyelid specimens from patients with congenital blepharoptosis showed a muscular dystrophy with loss of cross striations, decreased muscle fiber diameter, and fibrous and fatty displacement of the striated fibers. In specimens from patients with acquired blepharoptosis there was usually a disinsertion of the levator aponeurosis. Generally the muscles themselves were normal, although occasional specimens demonstrated myo-

genetic degeneration. In acquired blepharoptosis, reattachment of the disinserted aponeurosis to the tarsal plate is sufficient and surgery on the muscle itself is usually not required. In congenital blepharoptosis, however, the muscle itself is involved and some type of resection of tissue is necessary. (10 figures, 3 tables, 9 references)—David Shoch

JAMA

Diabetic retinopathy after two years of intensified insulin treatment. Kroc Collaborative Study Group. (Dept. Intern. Med., Yale Univ. School of Med., 333 Cedar St., New Haven, CT 06510). JAMA 260:37, 1988.

Sixty-eight patients with mild to moderate diabetic retinopathy were divided into two groups. Group A received intensified diabetic therapy with continuous subcutaneous insulin infusion and Group B continued to receive conventional injections. About one third of the patients in each group were changed to the other treatment at the end of the first eight months of study. After eight months it appeared that the group using continuous infusion had more advanced retinopathy than those receiving more conventional therapy. However, over the next 16 months the degree of retinopathy increased in the conventionally treated group and decreased in the group receiving continuous infusion. After two years the degree of retinopathy was the same in the two groups. Thus, although there appears to be an initial acceleration of the retinopathy with tightened control, the phenomenon does not persist. (3 figures, 3 tables, 17 references)— David Shoch

Journal of Pediatric Ophthalmology and Strabismus

Reoperation rate in adjustable strabismus surgery. Wisnicki, H. J., Repka, M. X., and Guyton, D. L. (Wilmer B1-35, Johns Hopkins Hosp., 600 N. Wolfe St., Baltimore, MD 21205). J. Pediatr. Ophthalmol. Strabismus 25:112, 1988.

Because results of the surgical correction of strabismus are variable, a technique was previously devised in which a loop of suture is left exposed to be adjusted after the surgery. In

determining whether this adjustable suture in the postoperative period has reduced the rate of required reoperations, the authors reviewed 290 strabismus procedures, all of which were done by two surgeons. The reoperation rate was 9.7%. In a similar series performed by the authors in which adjustable sutures were not placed, the reoperation rate was 19%. Therefore, there does seem to be an improvement in the required reoperation rate with adjustable strabismus surgery. (1 figure, 1 table, 12 references)—David Shoch

Journal of Pediatrics

Ocular involvement in hemolytic-uremic syndrome. Siegler, R. I., Brewer, E. D., and Swartz, M. (Univ. Utah Medical Center, 50 N. Medical Dr., Salt Lake City, UT 84132). J. Pediatr. 112:594, 1988.

A 16-month-old boy with hemolytic-uremic developed thrombotic syndrome angiopathy following an episode of severe gastroenteritis. Magnetic resonance imaging showed multiple infarcts of the basal ganglia and deep white matter. There were no abnormalities of the optic pathways from the lateral geniculate to the occipital cortex. However, examination of the fundi showed bilateral optic atrophy and ischemic retinas with numerous cotton-wool spots. Fluorescein angiography demonstrated obstruction of branches of the retinal arteries with large areas of retinal nonperfusion and leakage of fluorescein into the vitreous. Fluorescein stained the walls of the major retinal vessels, which suggested endothelial cell damage. The cotton-wool spots suggested infarction of the retinal nerve fiber layer, probably secondary to obstruction of the retinal circulation. The patient probably had platelet-fibrin thrombi similar to those found in renal vessels. Various treatments have been suggested, but as yet there is no specific therapy available to reverse the ocular involvement in the thrombotic microangiography of the hemolytic-uremic syndrome. (2 figures, 13 references)—David Shoch

Retina

Retinal arteriolar changes in patients with hyperlipidemias. Orlin, C., Lee, K., Jampol, L., and

Farber, M. (303 E. Chicago Ave., Chicago, IL 60611). Retina 8:6, 1988.

In a masked fashion, fundus photographs of 26 patients with hyperlipidemia were compared with those of 22 normal patients and 35 patients with contralateral branch vein occlusion to identify any differences in arteriovenous nicking, narrowing, or tortuosity of the vessels. In patients with branch vein occlusions, the uninvolved eye was used for comparison. There were no differences in the retinal arterioles between patients with hyperlipidemia and the control group. However, patients with branch retinal vein occlusions in the contralateral eye had greater arteriovenous nicking than patients in the control group or the group with hyperlipidemia. Examination of these retinal vascular parameters is not helpful in detecting hyperlipidemia. (3 tables, 9 references)— David Shoch

Refractive changes from use of silicone oil in vitreous surgery. Stefansson, E., Anderson, M. M., Landers, M. B., Tiedeman, J. S., and McCuen, B. W. (Duke Univ. Eye Ctr., Box 3802, Durham, NC 27710). Retina 8:20, 1988.

Aphakia is frequently treated by placing lenses of plus power in front of the eye, on the cornea, or inside the eye. It has been theorized that if a material of refractive index higher than the vitreous is used, the hyperopia produced by aphakia might also be reduced. This is true if silicone oil (refractive index, 1.405) is used to replace vitreous (refractive index, 1.336). In a review of eight aphakic eyes with silicone oil,

there was a marked shift toward the myopic side of 5 to 13 diopters. Conversely, in one pseudophakic and two phakic patients, the eyes became 3 to 10 diopters more hyperopic. This variation is dependent in part on such factors as severe myopia or incomplete silicone oil filling. It is essential to recognize these changes in the postoperative period in order to obtain maximum visual acuity. (2 figures, 1 table, 5 references)—David Shoch

Science

Tandem array of human visual pigment genes at Xq28. Vollrath, D., Nathans, J., and Davis, R. W. (Dept. Biochem., Stanford Univ. School of Med., Stanford, CA 94305). Science 240:1669, 1988.

In a series of 25 patients with red or green color blindness, 24 patients showed derangment in at least one gene. There is usually either a gene deletion or a fusion of genes. The authors mapped the gene array in four patients with red-green color deficiency and found support for a model that specifies a head-to-tail tandem array of genes, with the red pigment gene at the end and a variable number of green pigment genes near by. Homologous but unequal crossing over in the array would generate the variation in the number of green pigment genes seen in normal subjects and also explain the gene fusions and deletions observed in color-blind individuals. The red pigment gene is never duplicated or deleted because of its position at the end of the array. (4 figures, 17 references)—David Shoch

NEWS ITEMS

Send News Items to American Journal of Ophthalmology 435 N. Michigan Ave., Suite 1415 Chicago, IL 60611

The Journal invites readers to submit announcements concerning meetings, postgraduate courses, lectures, honors, and appointments. Each item must be typed double-spaced on bond paper with 1½-inch margins. Only one news item should be submitted on each page. Announcements concerning meetings and courses must contain the title, location, dates, sponsors, and address required for additional information. Each item must not exceed 75 words in length. Announcements of meetings and courses must be received at least four months before the event.

XVII Congress of the Pan American Association of Ophthalmology

The XVII Congress of the Pan American Association of Ophthalmology and the XXV Brazilian Congress of Ophthalmology will meet in Rio de Janeiro, Sept. 3–6, 1989. Dr. Adalmir Mortera Dantas is president of the XXV Brazilian Congress and Dr. Rubens Belfort, Jr., is president of the Pan American Association of Ophthalmology. Information is available from the Pan American Association of Ophthalmology, 1301 S. Bowen Rd., Suite 365, Arlington, TX 76013 or from the Congresso Panamericano y Brasilero de Oftalmologia, L.K. - R. Costa Pereira, 9, 20511 - Rio de Janeiro, Brasil.

American Academy of Ophthalmology: Future Meetings

Future meetings of the American Academy of Ophthalmology are as follows:

Oct. 8–12, 1988—Las Vegas, Nevada

Oct. 29–Nov. 2, 1989—New Orleans Oct. 28–Nov. 1, 1990—Atlanta

Oct. 13–17, 1991—Anaheim

Nov. 8–12, 1992—Dallas Nov. 14–18, 1993—Chicago

Oct. 30-Nov. 3, 1994—San Francisco

Oct. 29-Nov. 2, 1995—Atlanta

Oct. 6–10, 1996—Chicago

Oct. 26–30, 1997—San Francsico Nov. 8–12, 1998—New Orleans

German Ophthalmological Society: International Symposium on Tumors of the Eye

The German Ophthalmological Society will sponsor an International Symposium on Tumors of the Eye, Sept. 20-23, 1989, in Essen,

West Germany. For further information, write Universitatsklinikum Essen, Office of the University Eye Hospital, Hufelandstrasse 55, D 4300 Essen 1, West Germany.

The Seventh Canadian Interdisciplinary Conference on the Visually Impaired Child

The Seventh Canadian Interdisciplinary Conference on the Visually Impaired Child will be held Nov. 12–15, 1988, in Toronto, Canada. For further information, write Caprice Lamothe, Conference Coordinator, 1929 Bayview Ave., Toronto, Ontario, Canada M4G 3E8.

Canadian Implant Association: Sixth Annual Meeting

The Canadian Implant Association will hold its Sixth Annual Meeting, Dec. 27–29, 1988, in Hollywood, Florida. For further information, write M. L. Kwitko, 5591 Cote des Neiges Rd., Suite 1, Montreal, Canada H3T 1Y8.

Cullen Eye Institute: The Cullen Course 1989

The Cullen Eye Institute will present The Cullen Course 1989, Clinical Advances in Ophthalmology for the Practicing Ophthalmologist, March 17–19, 1989, in Houston, Texas. For further information, write Carol J. Soroka, Program Coordinator, Office of Continuing Education, Baylor College of Medicine, One Baylor Plaza, Houston, TX 77030.

Donald W. Dulaney Foundation: Advanced Aspen Anterior Segment Seminar

The Donald W. Dulaney Foundation for Ophthalmic Research and Education will sponsor the Advanced Aspen Anterior Segment Seminar, Feb. 27–March 3, 1989, in Aspen, Colorado. For further information, write Sharlee Dodd, Conference Coordinator, Donald W. Dulaney Foundation, P.O. Box 2337, Sun City, AZ 85373.

Doheny Eye Institute: Controversies in Ophthalmology Course

The Doheny Eye Institute will sponsor a course, Controversies in Ophthalmology, Nov. 17 and 18, 1988, in Los Angeles, California. For further information, write Maria Bing, Continuing Medical Education, Doheny Eye Institute, 1355 San Pablo St., Los Angeles, CA 90033.

Massachusetts Eye and Ear Infirmary: Neurology of the Anterior Visual Pathway

The Massachusetts Eye and Ear Infirmary will sponsor a course, Neurology of the Anterior Visual Pathway, Dec. 17, 1988, in Boston, Massachusetts. For further information, write Harvard Medical School, Dept. of Continuing Education, 243 Charles St., Boston, MA 02115.

Aspen Corneal Society: Ninth Annual Meeting

The Aspen Corneal Society will hold its Ninth Annual Meeting, Feb. 18–25, 1989, in Snowmass, Colorado. For further information, write Mitchell H. Friedlaender, M.D., Division of Ophthalmology, Scripps Clinic and Research Foundation, 10666 N. Torrey Pines Rd., La Jolla, CA 92037.

Johns Hopkins Medical Institutions: The Management of Complicated Retinal Detachments

The Wilmer Institute of the Johns Hopkins Medical Institutions will present a course, The Management of Complicated Retinal Detachments, Nov. 4, 1988. For further information, write Office of Continuing Medical Education, The Johns Hopkins Medical Institutions, Turner 22, 720 Rutland Ave., Baltimore, MD 21205.

St. Vincent Charity Hosptial & Health Center: Small Incision Surgery

St. Vincent Charity Hospital & Health Center will sponsor a course, Small Incision Surgery: Phacoemulsification Techniques, Advances and Future Lens Materials, Nov. 11 and 12, 1988, in

Cleveland, Ohio. For further information, write Brooke Simonds, Special Projects Coordinator, Associated Cataract & Laser Surgeons, Inc., 1500 N. Superior St., Toledo, OH 43604.

Pan American Association of Ophthalmology Appointment

The Pan American Association of Ophthalmology, has appointed Thomas Hunter Smith, M.D., as administrator and resource development officer for the Pan-American Association of Ophthalmology and the Pan-American Ophthalmological Educational Fund.

Personals .

Albert C. Esposito

The Cabell County Medical Society, Huntington, West Virginia, to honor Albert C. Esposito Esposito for being the founder of the Marshall University School of Medicine, voted to name each of their October meetings The Dr. Albert C. Esposito meeting.

Donald M. Gass

Donald M. Gass received the first J. Donald M. Gass Medal of the Macula Society.

Harvey A. Lincoff

At the annual meeting of the Retina Society, the Award of Merit in retina research was presented to Harvey A. Lincoff.

Arnall Patz

The first Arnall Patz Medal of the Macula Society was presented recently to Arnall Patz.



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Robert C. Maynor, Jr., MD, F.A.

Robt Maynor u

October 5, 1987. Huntsville, AL



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